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(54) Title: SPIROCYCLIC PIPERIDINES AS MCH1 ANTAGONISTS AND USES THEREOF

(57) Abstract: This invention is directed to compounds which are selective antagonists for melanin concentrating hormone-1 (MCH1) receptors. The invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier. This invention provides a pharmaceutical composition made by combining a therapeutically effective amount of the compound of this invention and a pharmaceutically acceptable carrier. This invention further provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier. This invention also provides a method of reducing the body mass of a subject which comprises administering to the subject an amount of a compound of the invention effective to reduce the body mass of the subject. This invention further provides a method of treating a subject suffering from depression and/or anxiety which comprises administering to the subject an amount of a compound of the invention effective to treat the subject=s depression and/or anxiety. This invention further provides a method of treating a subject suffering from a urinary disorder.

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SPIROCYCLIC PIPERIDINES AS MCH1 ANTAGONISTS AND USES THEREOF

This application claims priority of U.S. Serial No. 10/189,146, filed July 3, 2002, the contents of which are hereby incorporated by reference.

Throughout this application, various publications are referenced in parentheses by author and year. Full citations for these references may be found at the end of the specification immediately preceding the claims.

The disclosure of these publications in their entireties are hereby incorporated by reference into this application to describe more fully the state of the art to which this invention pertains.

BACKGROUND OF THE INVENTION

Melanin-concentrating hormone (MCH) is a cyclic peptide originally isolated from salmonid (teleost fish) pituitaries (Kawauchi et al., 1983). In fish the 17 amino acid peptide causes aggregation of melanin within the melanophores and inhibits the release of ACTH, acting as a functional antagonist of -MSH. Mammalian MCH (19 amino acids) is highly conserved between rat, mouse, and human, exhibiting 100% amino acid identity, but its physiological roles are less clear. MCH has been reported to participate in a variety of processes including feeding, water balance, energy metabolism, general arousal/attention state, memory and cognitive functions, and psychiatric disorders (for reviews, see Baker, 1991; Baker, 1994; Nahon, 1994; Knigge et al., 1996). Its role in feeding or body weight regulation is supported by a recent *Nature* publication (Qu et al., 1996) demonstrating that MCH is overexpressed in the hypothalamus of *ob/ob* mice compared with *ob/+* mice, and that fasting further increased MCH mRNA in both obese and normal mice during fasting. MCH also stimulated feeding in normal rats when injected into the lateral ventricles (Rossi et al., 1997).

MCH also has been reported to functionally antagonize the behavioral effects of -MSH (Miller et al., 1993; Gonzalez et al, 1996; Sanchez et al., 1997); in addition, stress has been shown to increase POMC mRNA levels while decreasing the MCH precursor preproMCH (ppMCH) mRNA levels (Presse et al., 1992). Thus MCH may serve as an integrative neuropeptide involved in the reaction to stress, as well as in the regulation of feeding and sexual activity (Baker, 1991; Knigge et al., 1996).

The biological effects of MCH are believed to be mediated by specific receptors. A tritiated ligand ([^{3}H]-MCH) was reported to exhibit specific binding to brain membranes but was unusable for saturation analyses, so neither affinity nor B_{max} were determined (Drozdz and Eberle, 1995). Radioiodination of the tyrosine at position thirteen resulted in a ligand with dramatically reduced biological activity (see Drozdz and Eberle, 1995). In contrast, the radioiodination of the MCH analogue [Phe^{13},Tyr^{19}]-MCH was successful (Drozdz et al., 1995); the ligand retained biological activity and exhibited specific binding to a variety of cell lines including mouse melanoma (B16-F1, G4F, and G4F-7), PC12, and COS cells. In G4F-7 cells, the K_D = 0.118nM and the B_{max} ~1100 sites/cell. Importantly, the binding was not inhibited by -MSH but was weakly inhibited by rat ANF (Ki = 116 nM vs. 12 nM for native MCH) (Drozdz et al., 1995). More recently specific MCH binding was reported in transformed keratinocytes (Burgaud et al., 1997) and melanoma cells (Drozdz et al., 1998), where photo-crosslinking studies suggest that the receptor is a membrane protein with an apparent molecular weight of 45-50 kDaltons, compatible with the molecular weight range of the GPCR superfamily of receptors. No radioautoradiographic studies of MCH receptor localization using this ligand have been reported as yet.

The localization and biological activities of MCH peptide suggest that the modulation of MCH receptor activity may be useful in a number of therapeutic applications. The role of MCH in feeding is the best characterized of its potential clinical uses. MCH is expressed in the lateral hypothalamus, a brain area implicated in the regulation of thirst and hunger (Grillon et al., 1997); recently orexins A and B, which are potent orexigenic agents, have been shown to have very similar localization to MCH in the lateral hypothalamus (Sakurai et al., 1998). MCH mRNA

levels in this brain region are increased in rats after 24 hours of food-deprivation (Hervé and Fellman, 1997); after insulin injection, a significant increase in the abundance and staining intensity of MCH immunoreactive perikarya and fibres was observed concurrent with a significant increase in the level of MCH mRNA (Bahjaoui-Bouhaddi et al., 1994).

Consistent with the ability of MCH to stimulate feeding in rats (Rossi et al., 1997) is the observation that MCH mRNA levels are upregulated in the hypothalami of obese *ob/ob* mice (Qu et al., 1996), and decreased in the hypothalami of rats treated with leptin, whose food intake and body weight gains are also decreased (Sahu, 1998). MCH appears to act as a functional antagonist of the melanocortin system in its effects on food intake and on hormone secretion within the HPA (hypothalamopituitary/adrenal axis) (Ludwig et al., 1998). Together these data suggest a role for endogenous MCH in the regulation of energy balance and response to stress, and provide a rationale for the development of specific compounds acting at MCH receptors for use in the treatment of obesity and stress-related disorders.

In all species studied to date, a major portion of the neurons of the MCH cell group occupies a rather constant location in those areas of the lateral hypothalamus and subthalamus where they lie and may be a part of some of the so-called "extrapyramidal" motor circuits. These involve substantial striato- and pallidofugal pathways involving the thalamus and cerebral cortex, hypothalamic areas, and reciprocal connections to subthalamic nucleus, substantia nigra, and mid-brain centers (Bittencourt et al., 1992). In their location, the MCH cell group may offer a bridge or mechanism for expressing hypothalamic visceral activity with appropriate and coordinated motor activity. Clinically it may be of some value to consider

the involvement of this MCH system in movement disorders, such as Parkinson=s disease and Huntingdon's Chorea in which extrapyramidal circuits are known to be involved.

Human genetic linkage studies have located authentic hMCH loci on chromosome 12 (12q23-24) and the variant hMCH loci on chromosome 5 (5q12-13) (Pedeutour et al., 1994). Locus 12q23-24 coincides with a locus to which autosomal dominant cerebellar ataxia type II (SCA2) has been mapped (Auburger et al., 1992; Twells et al., 1992). This disease comprises neurodegenerative disorders, including an olivopontocerebellar atrophy.

Furthermore, the gene for Darier's disease, has been mapped to locus 12q23-24 (Craddock et al., 1993). Darier's disease is characterized by abnormalities I keratinocyte adhesion and mental illnesses in some families. In view of the functional and neuroanatomical patterns of the MCH neural system in the rat and human brains, the MCH gene may represent a good candidate for SCA2 or Darier's disease. Interestingly, diseases with high social impact have been mapped to this locus. Indeed, the gene responsible for chronic or acute forms of spinal muscular atrophies has been assigned to chromosome 5q12-13 using genetic linkage analysis (Melki et al., 1990; Westbrook et al., 1992). Furthermore, independent lines of evidence support the assignment of a major schizophrenia locus to chromosome 5q11.2-13.3 (Sherrington et al., 1988; Bassett et al., 1988; Gilliam et al., 1989). The above studies suggest that MCH may play a role in neurodegenerative diseases and disorders of emotion.

Additional therapeutic applications for MCH-related compounds are suggested by the observed effects of MCH in other biological systems. For example, MCH may regulate reproductive functions in male and female rats. MCH transcripts and MCH peptide were found within germ cells

in testes of adult rats, suggesting that MCH may participate in stem cell renewal and/or differentiation of early spermatocytes (Hervieu et al., 1996). MCH injected directly into the medial preoptic area (MPOA) or ventromedial nucleus (VMN) stimulated sexual activity in female rats (Gonzalez et al., 1996). In ovariectomized rats primed with estradiol, MCH stimulated luteinizing hormone (LH) release while anti-MCH antiserum inhibited LH release (Gonzalez et al., 1997). The zona incerta, which contains a large population of MCH cell bodies, has previously been identified as a regulatory site for the pre-ovulatory LH surge (MacKenzie et al., 1984).

MCH has been reported to influence release of pituitary hormones including ACTH and oxytocin. MCH analogues may also be useful in treating epilepsy. In the PTZ seizure model, injection of MCH prior to seizure induction prevented seizure activity in both rats and guinea pigs, suggesting that MCH-containing neurons may participate in the neural circuitry underlying PTZ-induced seizure (Knigge and Wagner, 1997). MCH has also been observed to affect behavioral correlates of cognitive functions. MCH treatment hastened extinction of the passive avoidance response in rats (McBride et al., 1994), raising the possibility that MCH receptor antagonists may be beneficial for memory storage and/or retention. A possible role for MCH in the modulation or perception of pain is supported by the dense innervation of the periaqueductal grey (PAG) by MCH-positive fibers. Finally, MCH may participate in the regulation of fluid intake. ICV infusion of MCH in conscious sheep produced diuretic, natriuretic, and kaliuretic changes in response to increased plasma volume (Parkes, 1996). Together with anatomical data reporting the presence of MCH in fluid regulatory areas of the brain, the results indicate that MCH may be an important peptide involved in the central control of fluid homeostasis in mammals.

The identification of a G-protein coupled receptor for MCH has recently been published (Chambers et al., 1999; Saito et al., 1999). These groups identified MCH as the endogenous ligand for the human orphan G-protein coupled receptor SLC-1 (Lakaye et al., 1998). The rat homologue of this receptor (now called MCH-1) was reported to be localized in regions of the rat brain associated with feeding behavior (e.g. dorsomedial and ventromedial hypothalamus). The link between MCH-1 and the effects of MCH on feeding has been strengthened by recent reports on the phenotype of MCH-1 knockout mice. Two groups have shown independently (Marsh et al, 2002; Chen et al, 2002) that the targeted disruption of the MCH-1 receptor gene (MCH-1 knockout) in mice results in animals that are hyperphagic but are lean and have decreased body mass relative to wild-type littermates. The decrease in body mass is attributed to an increase in metabolism. Each group demonstrated that the MCH-1 knockout mice are resistant to diet-induced obesity, and generally exhibit weights similar to littermates maintained on regular chow.

Finally, synthetic antagonist molecules for the MCH-1 receptor have now been described in the literature. Bednarek et al. (2002) have reported on the synthesis of high affinity peptide antagonists of MCH-1. In addition, a small molecule antagonist of MCH-1 has been described by Takekawa et al. (Takekawa et al., 2002). This compound, T-226296, exhibits high affinity for the MCH-1 receptor (~5-9 nM for rat and human MCH-1), and was shown to inhibit food intake induced by the intracerebroventricular application of MCH. These data validate the strategy of using an MCH-1 receptor antagonist to treat obesity.

Furthermore, in our own studies, we have tested MCH1 antagonists in several animal models that are well known as predictive for the efficacy of compounds in humans

(Borowsky, et al., Nature Medicine 2003). These experiments indicate that MCH1 antagonists are useful to treat obesity, depression, anxiety, as well as urinary disorders.

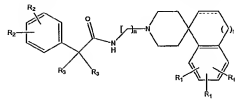
Herein, we report the synthesis of secondary amino anilinic piperidines that bind to the cloned human melanin-concentrating hormone-1 (MCH1) receptor. Additionally, these compounds selectively bind to the MCH1-receptor against other cloned G-protein coupled receptor. The ability to inhibit the activation of the cloned receptor as measured in *in vitro* assays is disclosed.

Furthermore, the compounds of the present invention may also be used to treat abnormal conditions mediated by inactivation of the MCH-1 receptor such as feeding disorders (obesity, bulimia and bulimia nervosa), sexual/reproductive disorders, depression, anxiety, depression and anxiety, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, sleep disturbances, or any condition in which antagonism of an MCH1 receptor may be beneficial.

In addition, the compounds of the present invention may be used to reduce the body mass of a subject. Furthermore, the compounds of the present invention may be used to treat urinary disorders.

Summary of the Invention

This invention provides a compound having the structure:



;

wherein ----- is CH_2, O, -CO-, $-CO_2-$, $-CH_2-CH_2-$ or -CHCH-;

wherein t is 0 or 1, and where the cyclic ring containing t is 5 or 6-membered;

wherein n is an integer from 1 to 6 inclusive;

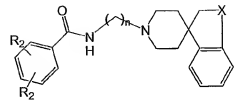
wherein each R_1 and R_2 is independently -H, -F, -Cl, -Br, -I; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, aryl or heteroaryl;

wherein each R_3 is independently -H; C_1-C_6 straight chained or branched alkyl; aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-R_2$, straight chained or branched C_1-C_7 alkyl, aryl, phenoxy or heteroaryl; and

where two R_3 moieties taken together can form a C_3-C_6 cycloalkyl;

or a pharmaceutically acceptable salt thereof.

This invention further provides a compound having the structure:



;

wherein each R_2 is independently H, F, Cl, Br, CN or C_1-C_7 straight chained or branched alkyl;

wherein X is CH_2 or O; and

wherein n is an integer from 1 to 6 inclusive.

Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of any one the compounds of the invention.

An illustration of the invention is a pharmaceutical composition made by admixing any one of the compounds described above and a pharmaceutically acceptable carrier.

Illustrative of the invention is a process for making a pharmaceutical composition comprising admixing any of the compounds of the invention and a pharmaceutically acceptable carrier.

Illustrative of the invention is a synthetic process for making any of the compounds of the invention.

Exemplifying the invention is a method of treating a disorder mediated by the MCH1 receptor in a subject in need thereof comprising administering to the subject a

therapeutically effective amount of any one of the compounds or pharmaceutical compositions of the invention and a pharmaceutically acceptable carrier.

In one embodiment, the therapeutically effective amount is between about 0.03 and about 300 mg.

In one embodiment, the disorder is depression. In one embodiment, the disorder is anxiety.

In one embodiment, the disorder is obesity.
In one embodiment, the disorder is urge incontinence.

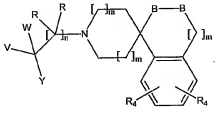
One embodiment is a method of treating a subject suffering from a disorder selected from depression, anxiety, obesity or urge incontinence in a subject in need thereof, comprising administering to a subject a therapeutically effective amount of a compound of the invention.

In one embodiment, the therapeutically effective amount is between about 0.03 and about 300 mg.

In another embodiment, the disorder is depression.
In one embodiment, the disorder is anxiety.
In one embodiment, the disorder is obesity.
In one embodiment, the disorder is urge incontinence.

Detailed Description of the Invention

The invention provides a compound having the structure:



wherein each B is independently CH_2, O or NH, with the proviso that if one B is either O or NH then the other B is CH_2;

wherein V is hydrogen, aryl, phenoxy or heteroaryl, wherein the aryl, phenoxy or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-ZR_3$, $-ZOR_3$, $-OZR_3$, $-ZN(R_3)_2$, $-N(R_3)ZR_3$, $-N(R_3)ZN(R_3)_2$, -CN, $-NO_2$, $-SR_3$, $-(CH_2)_qOR_3$, $-(CH_2)_qSR_3$, aryl, phenoxy or heteroaryl, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein W is hydrogen, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-ZR_3$, $-ZOR_3$, $-OZR_3$, $-ZN(R_3)_2$, $-N(R_3)ZR_3$, $-N(R_3)ZN(R_3)_2$, -CN, $-NO_2$, $-SR_3$, $-OR_3$, $-(CH_2)_qOR_3$, $-(CH_2)_qSR_3$, aryl, heteroaryl, phenoxy, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

wherein Y is hydrogen, =O (carbonyl oxygen), OR_3, =NNHV, $=NN(R_3)_2$, $-ZOR_3$, $-OZR_3$, $-ZN(R_3)_2$, $-N(R_3)ZR_3$, $-N(R_3)ZC(R_3)_3$ or -

$N(R_3)ZN(R_3)_2$, with the proviso that if Y is =O (carbonyl oxygen), =NNHV or $=NN(R_3)_2$, then W does not exist;

wherein Z is CO; CS; SO_2 or null;

wherein each R is independently -H, -F, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, $-N(R_3)_2$, $-NO_2$, -CN, $-CO_2R_3$, $-OCOR_3$, $-OR_3$, or $-N(R_3)COR_3$, $-CON(R_3)_2$;

wherein each R_2 is independently -H, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C, alkenyl or alkynyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-NO_2$, -CN;

wherein each R_3 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-N(R_2)_2$, $-NO_2$, -CN, $-COR_2$ $-CO_2R_2$, $-OCOR_2$, $-OR_2$, $-N(R_2)COR_2$ $-CON(R_2)_2$, straight chained or branched C_1-C_7 alkyl, aryl, phenoxy, benzyl or heteroaryl, wherein the aryl, phenoxy, benzyl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, -straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl or C_3-C_7 cycloalkyl,

monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein each R_4 is independently -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-NO_2$, -CN; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl or when two R_4 groups are adjacent to each other to form a methylenedioxy bond;

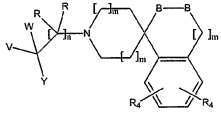
wherein each m is independently an integer from 0 to 1 inclusive;

wherein n is an integer from 0 to 6 inclusive;

wherein q is an integer from 1 to 3 inclusive;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



wherein each B is independently CO, O or NH, with the proviso that if one B is either O or NH then the other B is CO, and with the proviso that if one B is CO, then the other B is O or NH;

wherein V is hydrogen, aryl, phenoxy or heteroaryl, wherein the aryl, phenoxy or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-ZR_3$, $-ZOR_3$,

$-OZR_3$, $-ZN(R_3)_2$, $-N(R_3)ZR_3$, $-N(R_3)ZN(R_3)_2$, $-CN$, $-NO_2$, $-SR_3$, $-(CH_2)_qOR_3$, $-(CH_2)_qSR_3$, aryl, phenoxy or heteroaryl, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein W is hydrogen, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-ZR_3$, $-ZOR_3$, $-OZR_3$, $-ZN(R_3)_2$, $-N(R_3)ZR_3$, $-N(R_3)ZN(R_3)_2$, $-CN$, $-NO_2$, $-SR_3$, $-OR_3$, $-(CH_2)_qOR_3$, $-(CH_2)_qSR_3$, aryl, heteroaryl, phenoxy, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

wherein Y is hydrogen, =O (carbonyl oxygen), OR_3, =NNHV, $=NN(R_3)_2$, $-ZOR_3$, $-OZR_3$, $-ZN(R_3)_2$, $-N(R_3)ZR_3$, $-N(R_3)ZC(R_3)_3$ or $-N(R_3)ZN(R_3)_2$, with the proviso that if Y is =O (carbonyl oxygen), =NNHV or $=NN(R_3)_2$, then W does not exist;

wherein Z is CO; CS; SO_2 or null;

wherein each R is independently -H, -F, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, $-N(R_3)_2$, $-NO_2$, $-CN$, $-CO_2R_3$, $-OCOR_3$, $-OR_3$, or $-N(R_3)COR_3$, $-CON(R_3)_2$;

wherein each R_2 is independently -H, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, aryl or heteroaryl, wherein the aryl or heteroaryl is

optionally substituted with one or more -F, -Cl, -Br, -I, $-NO_2$, -CN;

wherein each R_3 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-N(R_2)_2$, $-NO_2$, -CN, $-COR_2$ $-CO_2R_2$, $-OCOR_2$, $-OR_2$, $-N(R_2)COR_2$ $-CON(R_2)_2$, straight chained or branched C_1-C_7 alkyl, aryl, phenoxy, benzyl or heteroaryl, wherein the aryl, phenoxy, benzyl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, -straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein each R_4 is independently -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-NO_2$, -CN; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl or when two R_4 groups are adjacent to each other to form a methylenedioxy bond;

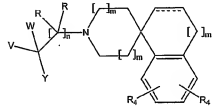
wherein each m is independently an integer from 0 to 1 inclusive;

wherein n is an integer from 0 to 6 inclusive;

wherein q is an integer from 1 to 3 inclusive;

or a pharmaceutically acceptable salt thereof.

The invention also provides a compound having the structure:



wherein the bond ----- indicates a single bond or double bond;

wherein V is hydrogen, aryl, phenoxy or heteroaryl, wherein the aryl, phenoxy or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-ZR_3$, $-ZOR_3$, $-OZR_3$, $-ZN(R_3)_2$, $-N(R_3)ZR_3$, $-N(R_3)ZN(R_3)_2$, -CN, $-NO_2$, $-SR_3$, $-(CH_2)_qOR_3$, $-(CH_2)_qSR_3$, aryl, phenoxy or heteroaryl, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein W is hydrogen, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-ZR_3$, $-ZOR_3$, $-OZR_3$, $-ZN(R_3)_2$, $-N(R_3)ZR_3$, $-N(R_3)ZN(R_3)_2$, -CN, $-NO_2$, $-SR_3$, $-OR_3$, $-(CH_2)_qOR_3$, $-(CH_2)_qSR_3$, aryl, heteroaryl, phenoxy, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

wherein Y is hydrogen, =O (carbonyl oxygen), OR_3, =NNHV, $=NN(R_3)_2$, $-ZOR_3$, $-OZR_3$, $-ZN(R_3)_2$, $-N(R_3)ZR_3$, $-N(R_3)ZC(R_3)_3$ or $-N(R_3)ZN(R_3)_2$, with the proviso that if Y is =O (carbonyl oxygen), =NNHV or $=NN(R_3)_2$, then W does not exist;

wherein Z is CO; CS; SO_2 or null;

wherein each R is independently -H, -F, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, $-N(R_3)_2$, $-NO_2$, -CN, $-CO_2R_3$, $-OCOR_3$, $-OR_3$, or $-N(R_3)COR_3$, $-CON(R_3)_2$;

wherein each R_2 is independently -H, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-NO_2$, -CN;

wherein each R_3 is independently -H; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-N(R_2)_2$, $-NO_2$, -CN, $-COR_2$ $-CO_2R_2$, $-OCOR_2$, $-OR_2$, $-N(R_2)COR_2$ $-CON(R_2)_2$, straight chained or branched C_1-C_7 alkyl, aryl, phenoxy, benzyl or heteroaryl, wherein the aryl, phenoxy, benzyl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, -straight chained or branched C_1-C_7 alkyl,

straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein each R_4 is independently -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, straight chained or branched C_1-C_7 alkyl, aryl, heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-NO_2$, -CN; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl or when two R_4 groups are adjacent to each other to form a methylenedioxy bond;

wherein each m is independently an integer from 0 to 1 inclusive;

wherein n is an integer from 0 to 6 inclusive;

wherein q is an integer from 1 to 3 inclusive;

or a pharmaceutically acceptable salt thereof.

In one embodiment, V is hydrogen, aryl, phenoxy or heteroaryl, wherein the aryl, phenoxy or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I;

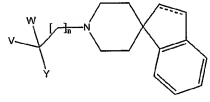
wherein W is hydrogen, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I;

wherein Y is hydrogen, =O (carbonyl oxygen), $-ZOR_3$, $-OZR_3$, $-ZN(R_3)_2$, $-N(R_3)ZR_3$, $-N(R_3)ZC(R_3)_3$ or $-N(R_3)ZN(R_3)_2$;

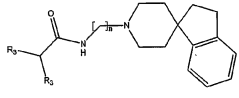
wherein each R is independently -H, -F, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

wherein each R_4 is independently -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, straight chained or branched C_1-C_7 alkyl.

In one embodiment, the compound has the structure:

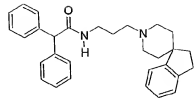


In one embodiment, the compound has the structure:

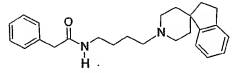


wherein each R_3 is independently -H, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-N(R_2)_2$, straight chained or branched C_1-C_7 alkyl, aryl, phenoxy, benzyl or heteroaryl, wherein the aryl, phenoxy, benzyl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, -straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

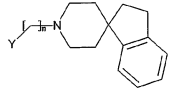
In one embodiment, the compound has the structure:



In one embodiment, the compound has the structure:



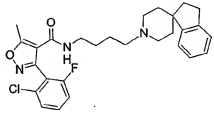
In one embodiment, the compound has the structure:



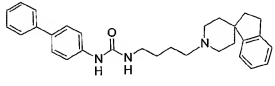
;

wherein Y is $-N(R_3)ZR_3$ or $N(R_3)ZN(R_3)_2$.

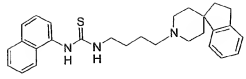
In one embodiment, the compound has the structure:



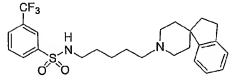
In one embodiment, the compound has the structure:



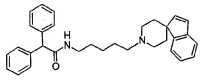
In one embodiment, the compound has the structure:



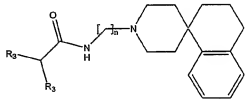
In one embodiment, the compound has the structure:



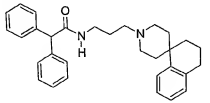
In one embodiment, the compound has the structure:



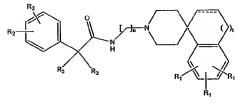
In one embodiment, the compound has the structure:



In one embodiment, the compound has the structure:



This invention further provides a compound having the structure:



;

wherein ----- is CH_2, O, -CO-, $-CO_2-$, $-CH_2-CH_2-$ or -CHCH-;

wherein t is 0 or 1, and where the cyclic ring containing t is 5 or 6-membered;

wherein n is an integer from 1 to 6 inclusive;

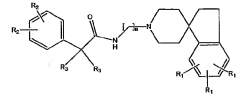
wherein each R_1 and R_2 is independently -H, -F, -Cl, -Br, -I; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, aryl or heteroaryl;

wherein each R_3 is independently -H; C_1-C_6 straight chained or branched alkyl; aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-R_2$, straight chained or branched C_1-C_7 alkyl, aryl, phenoxy or heteroaryl; and

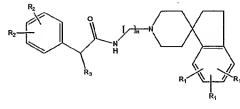
where two R_3 moieties taken together can form a C_3-C_6 cycloalkyl;

or a pharmaceutically acceptable salt thereof.

In one embodiment of the above invention, the compound has the structure:

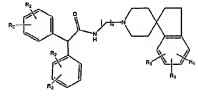


In one embodiment of the above invention, the compound has the structure:

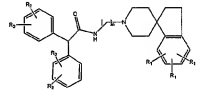


wherein R_3 is C_1-C_6 straight chained or branched alkyl or aryl, wherein the aryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-R_2$, straight chained or branched C_1-C_7 alkyl, aryl, phenoxy or heteroaryl.

In a further embodiment of the above invention, the compound has the structure:

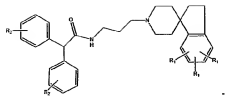


In a further embodiment of the above invention, the compound has the structure:

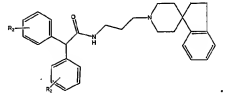


wherein each R_1 and R_2 is independently -H, -F, -Cl, -Br, -I; straight chained or branched C_1-C_7 alkyl, aryl or heteroaryl.

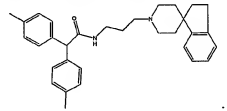
In one embodiment, the compound has the structure:



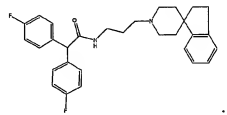
In one embodiment, the compound has the structure:



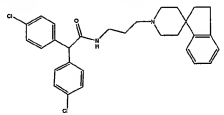
The compound having the structure:



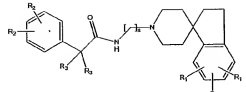
The compound having the structure:



The compound having the structure:



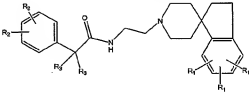
In yet another embodiment of the above described invention, the compound has the structure:



;

wherein each R_3 is independently H or C_1-C_6 straight chained or branched alkyl.

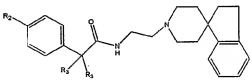
In one embodiment, the compound has the structure:



;

wherein each R_3 is C_1-C_6 straight chained or branched alkyl.

In one embodiment, the compound has the structure:

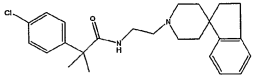


;

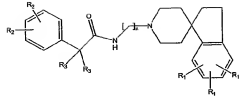
wherein each R_1 is F, Cl, Br or C_1-C_3 alkyl; and

wherein each R_3 is independently H or C_1-C_7 straight chained or branched alkyl.

The compound having the structure:



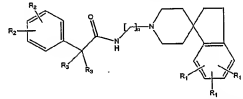
In yet another embodiment of the invention, the compound having the structure:



;

wherein the two R_3 moieties taken together form a C_3-C_6 cycloalkyl.

In one embodiment, the compound has the structure:

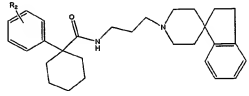


;

wherein the two R_3 moieties taken together form a C_4-C_6 cycloalkyl;

wherein each R_1 and R_2 is independently -H, -F, -Cl, -Br, -I; or straight chained or branched C_1-C_7 alkyl.

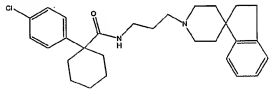
In one embodiment, the compound has the structure:



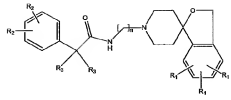
;

wherein R_2 is -H, -F, -Cl, -Br, -I.

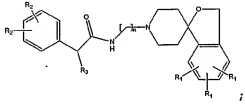
The compound having the structure:



In one embodiment, the compound has the structure:



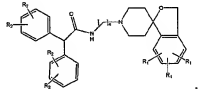
In one embodiment, the compound has the structure:



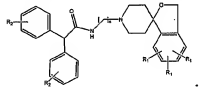
;

wherein R_3 is C_1-C_6 straight chained or branched alkyl or aryl wherein the aryl is optionally substituted with one or more -F, -Cl, -Br, -I, -R_2, straight chained or branched C_1-C_7 alkyl, aryl, phenoxy or heteroaryl.

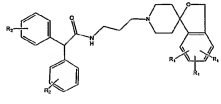
In one embodiment, the compound has the structure:



In one embodiment, the compound has the structure:



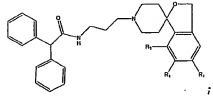
In one embodiment, the compound has the structure:



;

wherein each R_1 and R_2 is independently -H, -F, -Cl, -Br, -I; straight chained or branched C_1-C_7 alkyl.

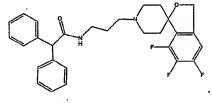
In one embodiment, the compound has the structure:



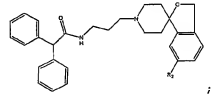
;

wherein each R_3 is independently -F, -Cl, -Br, -I; or straight chained or branched C_1-C_7 alkyl.

The compound having the structure:



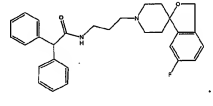
In one embodiment, the compound has the structure:



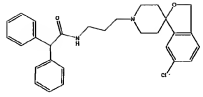
;

wherein R_1 is F, Cl, Br, I or C_1-C_7 straight chained or branched alkyl.

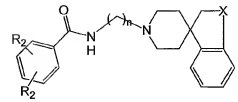
The compound having the structure:



The compound having the structure:



This invention further provides a compound having the structure:



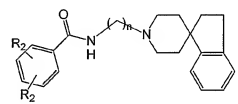
;

wherein each R_2 is independently H, F, Cl, Br, CN or C_1-C_7 straight chained or branched alkyl;

wherein X is CH_2 or O; and

wherein n is an integer from 1 to 6 inclusive.

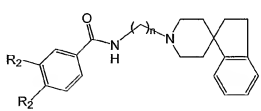
In one embodiment of the above-identified invention the compound has the structure:



;

wherein each R_2 is independently H, F, Cl or Br.

In one embodiment of the above-identified invention the compound has the structure:

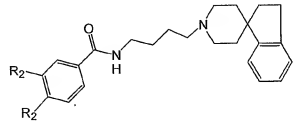


;

wherein each R_2 is independently H, F, Cl or Br; and

wherein n is an integer from 3 to 6 inclusive.

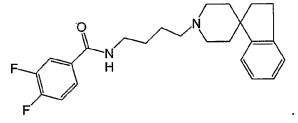
In one embodiment the compound has the structure:



;

wherein each R_2 is F, Cl or Br.

In one embodiment the compound has the structure:



Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of any one the compounds of the invention.

An illustration of the invention is a pharmaceutical composition made by admixing any one of the compounds described above and a pharmaceutically acceptable carrier.

Illustrative of the invention is a process for making a pharmaceutical composition comprising admixing any of the compounds of the invention and a pharmaceutically acceptable carrier.

Illustrative of the invention is a synthetic process for making any of the compounds of the invention.

Exemplifying the invention is a method of treating a disorder mediated by the MCH1 receptor in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any one of the compounds or pharmaceutical compositions of the invention and a pharmaceutically acceptable carrier.

In one embodiment, the therapeutically effective amount is between about 0.03 and about 300 mg.

In one embodiment, the disorder is depression. In one embodiment, the disorder is anxiety.

In one embodiment, the disorder is obesity.
In one embodiment, the disorder is urge incontinence.

One embodiment is a method of treating a subject suffering from a disorder selected from depression, anxiety, obesity or urge incontinence in a subject in need thereof, comprising administering to a subject a therapeutically effective amount of a compound of the invention.

In one embodiment, the therapeutically effective amount is between about 0.03 and about 300 mg.

In another embodiment, the disorder is depression.
In one embodiment, the disorder is anxiety.
In one embodiment, the disorder is obesity.
In one embodiment, the disorder is urge incontinence.

As used in the present above identified inventions, the term ''heteroaryl'' is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl

groups include, but are not limited to, carbazole, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

In addition, the term ''heteroaryl'' is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

The term ''heteroaryl'' also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, CN, $-NO_2$, straight chained or branched C_1-C_7 alkyl, straight chained or branched C_1-C_7 monofluoroalkyl, straight chained or branched C_1-C_7 polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl, straight chained or branched C_2-C_7 alkynyl; C_3-C_7 cycloalkyl, C_3-C_7 monofluorocycloalkyl, C_3-C_7 polyfluorocycloalkyl, C_5-C_7 cycloalkenyl,

The term ''heteroaryl'' further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

In the present invention, the term ''aryl'' is phenyl or naphthyl.

In a further embodiment of the aforementioned invention, the compound is enantiomerically and diasteriomerically pure.

In another embodiment, the compound is enantiomerically or diasteriomerically pure.

In one embodiment, the compound is a (+) enantiomer.

In one embodiment, the compound is a (-) enantiomer.

The invention provides for each pure stereoisomer of any of the compounds described herein. Such stereoisomers may include enantiomers, diastereomers, or E or Z alkene or imine isomers. The invention also provides for stereoisomeric mixtures, including racemic mixtures, diastereomeric mixtures, or E/Z isomeric mixtures. Stereoisomers can be synthesized in pure form (Nógrádi, M.; Stereoselective Synthesis, (1987) VCH Editor Ebel, H. and Asymmetric Synthesis, Volumes 3 B 5, (1983) Academic Press, Editor Morrison, J.) or they can be resolved by a variety of methods such as crystallization and chromatographic techniques (Jaques, J.; Collet, A.; Wilen, S.; Enantiomer, Racemates, and Resolutions, 1981, John Wiley and Sons and Asymmetric Synthesis, Vol. 2, 1983, Academic Press, Editor Morrison, J).

In addition the compounds of the present invention may be present as enantiomers, diasteriomers, isomers or two or more of the compounds may be present to form a racemic or diastereomeric mixture.

The compounds of the present invention are preferably 80% pure, more preferably 90% pure, and most preferably 95% pure. Included in this invention are pharmaceutically acceptable salts and complexes of all of the compounds described herein. The acids and bases from which these

salts are prepared include but are not limited to the acids and bases listed herein. The acids include, but are not limited to, the following inorganic acids: hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and boric acid. The acids include, but are not limited to, the following organic acids: acetic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, benzoic acid, glycolic acid, lactic acid and mandelic acid. The bases include, but are not limited to ammonia, methylamine, ethylamine, propylamine, dimethylamine, diethylamine, trimethylamine, triethylamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. This invention further provides for the hydrates and polymorphs of all of the compounds described herein.

The present invention includes within its scope prodrugs of the compounds of the invention. In general, such prodrugs will be functional derivatives of the compounds of the invention which are readily convertible in vivo into the required compound. Thus, in the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

The present invention further includes metabolites of the compounds of the present invention. Metabolites include active species produced upon introduction of compounds of this invention into the biological milieu.

Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of any one the compounds of the invention.

An illustration of the invention is a pharmaceutical composition made by admixing any one of the compounds described above and a pharmaceutically acceptable carrier.

Illustrative of the invention is a process for making a pharmaceutical composition comprising admixing any of the compounds of the invention and a pharmaceutically acceptable carrier.

A solid carrier can include one or more substances which may also act as endogenous carriers (e.g. nutrient or micronutrient carriers), flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinyl)pyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or

pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, coloring agents, viscosity regulators, stabilizers or osmoregulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate or isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be a halogenated hydrocarbon or other pharmaceutically acceptable propellent.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds may be prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium. Carriers are intended to include necessary and inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings. The compound can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters

of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

The compound can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspenions.

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

Illustrative of the invention is a synthetic process for making any of the compounds of the invention.

Exemplifying the invention is a method of treating a disorder mediated by the MCH1 receptor in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any one of the compounds or pharmaceutical compositions of the invention and a pharmaceutically acceptable carrier.

In one embodiment, the therapeutically effective amount is between about 0.03 and about 300 mg.

In one embodiment, the disorder is depression.

In one embodiment, the disorder is anxiety.

In one embodiment, the disorder is obesity.

In one embodiment, the disorder is urge incontinence.

One embodiment is a method of treating a subject suffering from a disorder selected from depression, anxiety, obesity or urge incontinence in a subject in need thereof, comprising administering to a subject a therapeutically effective amount of a compound of the invention.

In one embodiment, the therapeutically effective amount is between about 0.03 and about 300 mg.

In another embodiment, the disorder is depression.

In one embodiment, the disorder is anxiety.

In one embodiment, the disorder is obesity.

In one embodiment, the disorder is urge incontinence.

In the subject application a ''therapeutically effective amount'' is any amount of a compound which, when administered to a subject suffering from a disease against which the compounds are effective, causes reduction, remission, or regression of the disease. In a subject application, a ''subject'' is a vertebrate, a mammal or a human.

This invention provides a method of treating a subject suffering from an abnormality wherein the abnormality is alleviated by decreasing the activity of an MCH1 receptor which comprises administering to the subject an amount of a compound of the invention which is an MCH1 receptor antagonist effective to treat the subject's abnormality.

In separate embodiments, the abnormality is a regulation of a steroid or pituitary hormone disorder, an epinephrine release disorder, a gastrointestinal disorder, a cardiovascular disorder, an electrolyte balance disorder, hypertension, diabetes, a respiratory disorder, asthma, a reproductive function disorder, an immune disorder, an endocrine disorder, a musculoskeletal disorder, a neuroendocrine disorder, a cognitive disorder, a memory disorder such as Alzheimer=s disease, a sensory modulation and transmission disorder, a motor coordination disorder, a sensory integration disorder, a motor integration disorder, a dopaminergic function disorder such as Parkinson=s disease, a sensory transmission disorder, an olfaction disorder, a sympathetic innervation disorder, an affective disorder such as depression and anxiety, a stress-related disorder, a fluid-balance disorder, a seizure disorder, pain, psychotic behavior such as schizophrenia, morphine tolerance, opiate addiction, migraine or a urinary disorder such as urinary incontinence.

In a preferred embodiment, the subject invention provides a method of treatment for the following indications: depression, anxiety, eating/body weight disorders, and urinary disorders. Examples of eating/body weight disorders are obesity, bulimia, or bulimia nervosa. Examples of urinary disorders include, but are not limited to, urinary incontinence, overactive bladder, urge incontinence, urinary frequency, urinary urgency, nocturia, or enuresis. Overactive bladder and urinary urgency may or may not be associated with benign prostatic hyperplasia.

This invention provides a method of modifying the feeding behavior of a subject which comprises administering to the subject an amount of a compound of the invention effective to decrease the consumption of food by the subject.

This invention also provides a method of treating an eating disorder in a subject which comprises administering to the subject an amount of a compound of this invention effective to decrease the consumption of food by the subject. In an embodiment of the present invention, the eating disorder is bulimia, obesity or bulimia nervosa. In an embodiment of the present invention, the subject is a vertebrate, a mammal, a human or a canine. In a further embodiment, the compound is administered in combination with food.

The present invention further provides a method of reducing the body mass of a subject which comprises administering to the subject an amount of a compound of the invention effective to reduce the body mass of the subject.

The present invention also provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of a compound of this invention effective to treat the subject's depression. The present invention further provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of a compound of this invention effective to treat the subject's anxiety. The present invention also provides a method of treating a subject suffering from depression and anxiety which comprises administering to the subject an amount of a compound of this invention effective to treat the subject=s depression and anxiety.

The present invention also provides a method of treating a subject suffering from major depressive disorder, dysthymic disorder, bipolar I and II disorders, schizoaffective disorder, cognitive disorders with depressed mood, personality disorders, insomnia,

hypersomnia, narcolepsy, circadian rhythm sleep disorder, nightmare disorder, sleep terror disorder, sleepwalking disorder, obsessive-compulsive disorder, panic disorder, with or without agoraphobia, posttraumatic stress disorder, social anxiety disorder, social phobia and generalized anxiety disorder.

The present invention also provides a method of treating a subject suffering from a urinary disorder which comprises administering to the subject an amount of a compound of this invention effective to treat the subject's a urinary disorder. In some embodiments, the urinary disorder is urinary incontinence, overactive bladder, urge incontinence, urinary frequency, urinary urgency, nocturia, or enuresis.

This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

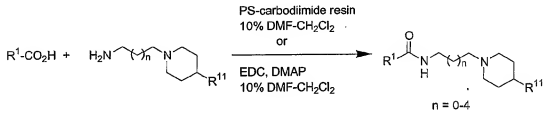
Experimental Section

I. Synthetic Methods for Examples

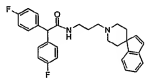
General Methods: All reactions (except for those done by parallel synthesis reaction arrays) were performed under an Argon atmosphere and the reagents, neat or in appropriate solvents, were transferred to the reaction vessel via syringe and cannula techniques. The parallel synthesis reaction arrays were performed in vials (without an inert atmosphere) using J-KEM heating shakers (Saint Louis, MO). Anhydrous solvents were purchased from Aldrich Chemical Company and used as received. The compounds described herein were named using the Nomenclator program (ChemInnovation Software, Inc. San Diego, CA). The ^{1}H NMR spectra were recorded at 400 MHz using a Brüker Avance spectrometer with tetramethylsilane as internal standard. Splitting patterns were designated as follows: s = singlet; d = doublet; t = triplet; q = quartet; quintet; sextet; septet; br = broad; m = multiplet. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. Mass spectra were obtained on a Platform II (Fisons) or Quattro Micro (Micromass) spectrometer with electrospray (ESMS) ionization and MH^+ is reported. Thin-layer chromatography (TLC) was carried out on glass plates precoated with silica gel 60 F_{254} (0.25 mm, EM Separations Tech.). Preparative thin-layer chromatography was carried out on glass sheets precoated with silica gel GF (2 mm, Analtech). Flash column chromatography was performed on Merck silica gel 60 (230 - 400 mesh). The microwave reactions were performed in a Smithcreator microwave apparatus from Personal chemistry Inc.

General Synthetic Procedures: The examples described in the experimental section are merely illustrative of the methods used to synthesize the present invention, i.e. MCH-1 antagonists. Additional compounds of the invention can be obtained by the general synthetic procedures described herein or by incorporating variations into these methods that would be obvious to someone skilled in the art.

Scheme E



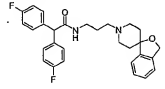
GENERAL PROCEDURE IN SCHEME E



2,2-BIS(4-FLUOROPHENYL)-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE. A solution of 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine (0.190 mmol, 46.0 mg), 2,2-bis(4-fluorophenyl)acetic acid (0.290 mmol, 72.0 mg), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.380 mmol, 334 mg) and 4-dimethylaminopyridine (catalytic amount) in DMF/CH_2Cl_2 (1:10, 5.0 mL) was stirred for 24 h at 23 °C. The solvent was removed *in vacuo* and the crude product was chromatographed (silica, dichoromethane:methanol 20:1) to afford the final product (23.6 mg, 26.3%). ^1H NMR (400

MHz, $CDCl_3$) δ 7.35-7.10 (m, 9H), 7.05-6.97 (m, 4H), 6.79 (d, 1H, J = 5.6 Hz), 6.75 (d, 1H, J = 5.6 Hz), 4.83 (s, 1H), 3.43 (dd, 2H, J = 6.0, 11.6 Hz), 2.98-2.90 (m, 2H), 2.53 (t, 2H, J = 6.6 Hz), 2.29 (t, 2H, J = 12.2 Hz), 2.10-1.96 (m, 2H), 1.80-1.70 (m, 2H), 1.34 (d, 2H, J = 13.2 Hz); ESMS m/e: 473.3 $(M + H)^+$.

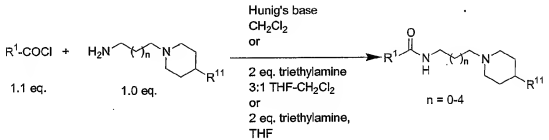
A library was constructed in polypropylene Robbins ''Reactor Blocks'', 48 well plates. In each plate an array of 6 amines (0.100 mmol) and 8 carboxylic acid (1.05 mmol) with PS-carbodiimide resin (2.0 mmol) and DMF:DCM (1:10 3.00 mL) were mixed overnight at 23 °C to give 48 compounds/plate. The reactions were rigorously monitored via TLC to the completion of the starting. The solvent was filtered and the resin was washed with methanol and dichloromethane (x3) alternately with each of the solvents (for 10 minutes each time). After the last filtration, 2.0 M ammonia in methanol was added to the resin (2.0 mL to each well) and the reaction blocks were rotated for 2 hours to release the desired compounds from the resin. The final compounds were filtered into Robbins ''Receiving Blocks'', the solvent was removed and the compounds were analyzed via NMR and ESMS.



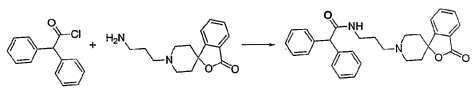
2,2-BIS(4-FLUOROPHENYL)-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE was prepared and purified from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine (49.2 mg, 0.200 mmol), 2,2-bis(4-fluorophenyl)acetic acid (0.220 mmol, 54.6 mg), PS-CDI (0.400 mmol, 0.300 g) and DMF/CH_2Cl_2 (0.3/3.0 mL) according

to the procedures described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.19 (m, 7H), 7.11-6.98 (m, 6H), 4.81 (s, 1H), 3.44-3.37 (m, 2H), 2.82-2.74 (m, 2H), 2.50-2.43 (m, 2H), 2.40-2.31 (m, 2H), 1.88-1.68 (m, 8H); ESMS m/e: 477.3 (M + H)$^+$.

Scheme F



GENERAL PROCEDURE IN SCHEME F



N-[3-(1-OXOSPIRO[1,3-HYDROISOBENZOFURAN-3,4'-PIPERIDINE]-10-YL)PROPYL]-2,2-DIPHENYLACETAMIDE. A solution of 10-(3-aminopropyl)spiro[3-hydroisobenzofuran-3,4'-piperidine]-1-one (37.0 mg, 0.100 mmol), 2,2-diphenylacetyl chloride (23.0 mg, 0.100 mmol) and diisopropylethylamine (0.200 mmol, 20.2 mg) in CH_2Cl_2 (or THF or THF/CH_2Cl_2, 2.0 mL) was stirred for 24 h at 23 °C. The solvent was removed *in vacuo* and the crude product was chromatographed (silica, dichoromethane:methanol 20:1) to afford the final product (20.3 mg, 41.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, 1H, J = 7.6 Hz), 7.83-7.69 (m, 1H), 7.69-7.55 (m, 3H), 7.49-7.37 (m, 4H), 7.37-7.26 (m, 4H), 7.26-7.16 (m, 2H), 5.20 (s,

1H), 3.57-3.42 (m, 2H), 3.41-3.25 (m, 2H), 3.17-2.98 (m, 4H), 2.98-2.81 (m, 2H), 2.26-2.02 (m, 2H), 1.80-1.61 (m, 2H); ESMS m/e: 455.3 $(M + H)^+$.

The Capture and Release Method for the Synthesis and Purification of the Spirocyclic Piperidine Library

The commercially obtained Amberlyst 15 exchange resin (Aldrich) was activated using the following procedure:

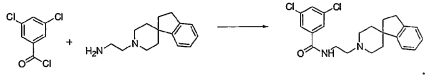
1. The resin was shaken in methanol for 24 hr.
2. The resin was filtered and washed with methanol on a fritted funnel.
3. The resin was neutralized with 2.0 M NH_3 in MeOH (pH checked) - shaken for 1 hr.
4. The neutralized resin was acidified with 3.0 M HCl in MeOH (pH checked) - shaken for 1 hr.
5. The resin was captured on a fritted funnel and washed with MeOH.
6. The resin was dried *in vacuo* and stored.

Synthesis (Acylation of the Amines):

A library was constructed in polypropylene Robbins ''Reactor Blocks'', 48 well plates. In each plate an array of 6 amines (0.100 mmol) and 8 electrophiles (acid chlorides, 1.50 eq) in the presence of triethylamine (2.00 eq) in THF:DCM 3:1 (2.00 mL) were mixed overnight at 23 °C to give 48 compounds/plate. The reactions were rigorously monitored via TLC to the completion of the starting amine due to the ensuing purification methodology via the acidic Amberlyst 15 resin. Following the disappearance of the starting amine, the desired products were captured and then released using the process outlined below.

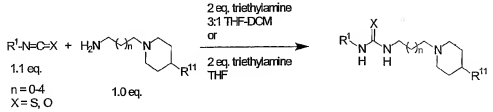
Purification of the Spirocyclic Piperidine Products:

Activated Amberlyst 15 ion-exchange resin (0.90 g, Aldrich) was added to each well, and the plates were rotated for 2 hours in a Robbins rotating oven to capture the desired final product from the reaction mixture. The solvent was filtered and the resin was washed with methanol and dichloromethane (x3) alternately with each of the solvents (for 10 minutes each time). After the last filtration, 2.0 M ammonia in methanol was added to the resin (2.0 mL to each well) and the reaction blocks were rotated for 2 hours to release the desired compounds from the resin. The final compounds were filtered into Robbins ''Receiving Blocks'', the solvent was removed and the compounds were analyzed via LCMS.



(3,5-DICHLOROPHENYL)-N-(2-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YLETHYL)CARBOXAMIDE was prepared and purified from 2-(-(SPIRO[indane-1,4'-piperidine]-10-ylethylamine (0.100 mmol, 23.0 mg) and 3,5-dichlorobenzoyl chloride (0.150 mmol, 65.0 mg) in THF/CH_2Cl_2 (3:1, 3.00 mL) according to the procedures described above. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, 1H, J = 1.8 Hz), 7.50 (t, 1H, J = 2.0 Hz), 7.24-7.14 (m, 5H), 7.05 (br, 1H), 3.61-3.54 (m, 2H), 3.00-2.85 (m, 4H), 2.68 (t, 2H, J = 6.0 Hz), 2.30 (t, 2H, J = 11.6 Hz), 2.10-1.90 (m, 4H), 1.59 (d, 2H, J = 12.4 Hz); ESMS m/e: 403.1 $(M + H)^+$.

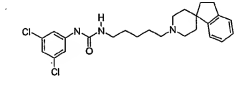
Scheme G



GENERAL PROCEDURE IN SCHEME G

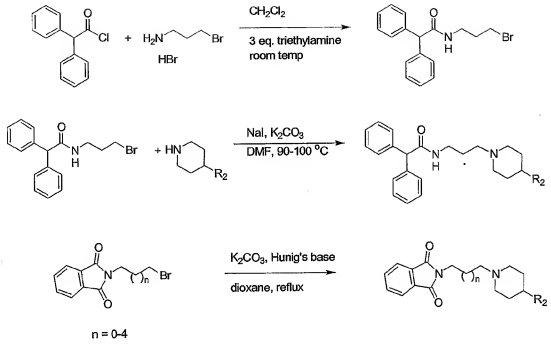
The library was constructed in polypropylene Robbins "Reactor Blocks", 48 well plates. In each plate an array of 6 amines (0.100 mmol) and 8 isocyanate (1.05 mmol) with triethylamine resin (2.0 mmol) and THF:DCM (1:1 3.00 mL) were mixed overnight at 23 °C to give 48 compounds/plate. The reactions were rigorously monitored via TLC to the completion of the starting.

Purification of the Spirocyclic Piperidine Products: Activated Amberlyst 15 ion-exchange resin (0.90 g, Aldrich) was added to each well, and the plates were rotated for 2 hours in a Robbins rotating oven to capture the desired final product from the reaction mixture. The solvent was filtered and the resin was washed with methanol and dichloromethane (x3) alternately with each of the solvents (for 10 minutes each time). After the last filtration, 2.0 M ammonia in methanol was added to the resin (2.0 mL to each well) and the reaction blocks were rotated for 2 hours to release the desired compounds from the resin. The final compounds were filtered into Robbins "Receiving Blocks", the solvent was removed and the compounds were analyzed via NMR and ESMS.



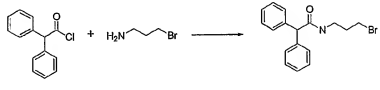
N-(3,5-DICHLOROPHENYL)[(5-(-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PENTYL)AMINO]CARBOXAMIDE (30.7 mg, 66.7%) was prepared from 5-(-(SPIRO[indane-1,4'-piperidine]-10-yl)pentylamine (0.100 mmol, 27.2 mg), 3,5-dichlorobenzenisocyanate (0.150 mmol, 28.2 mg), triethylamine (0.200 mmol, 20.2 mg) and THF:DCM (1:1 3.00 mL) according to the procedures described above. ESMS m/e: 460.1 $(M + H)^+$.

Scheme H


CH2Cl2
3 eq. triethylamine
room temp
HBr
NaI, K2CO3
DMF, 90-100 °C
K2CO3, Hunig's base
dioxane, reflux
n = 0-4

General Procedure in Scheme H

Procedure H1: A mixture of the spirocyclic piperidine (1.00 eq, 0.0226 mmol), *N*-(bromoalkyl)phthalimide (1.50 eq, 0.0338 mmol), Bu_4NI (200 mg) and diisopropylethylamine (5.00 eq, 0.113 mmol) in dioxane (200 mL) was heated at 95 °C for 24 hours. TLC analysis (silica . 95:5 dichloromethane:methanol) indicated the presence of some spirocyclic piperidine. Additional 0.0113 mmole of the appropriate bromoalkyl)phthalimides was added to each reaction mixture and heating was continued for additional 48 hours. The reaction mixture was cooled to room temperature, the ammonium salts were filtered out and the solvent was removed under reduced pressure. The crude product was chromatographed [3% NH_3 (2.0 M in methanol) in CH_2Cl_2] to give the desired product.

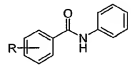


N-(3-BROMOPROPYL)-2,2-DIPHENYLACETAMIDE. A mixture of 2,2-diphenylacetic chloride (6.00 g, 26.0 mmol), 3-bromo-1-aminopropane hydrobromide (5.69 g, 26.0 mmol) and triethylamine (10.9 mL, 78.0 mmol) in dichloromethane (100 mL) was stirred at 25 °C for 24 hours. Water (100 mL) was added into the reaction mixture and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$

and concentrated under reduced pressure. The crude product was chromatographed (Hexanes:EtOAc 2:1) to afford the desired product (6.67 g, 77.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.30-7.17 (m, 10H), 6.64-6.55 (m, 1H), 4.86 (s, 1H), 3.29-3.19 (m, 4H), 1.95-1.85 (m, 2H); ESMS m/e: 332.21 $(M + H)^+$.

General Procedure for the Synthesis of the Substituted Spiro[1,3-dihydroisobenzofuran-1,4'-piperidine] (Scheme K):

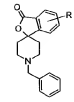
Substituted Phenyl-*N*-benzamide:



A mixture of 1 equivalent of a substituted benzoic acid, 3 equivalents of thionyl chloride and 5% DMF in dichloromethane (1M) were heated at reflux temperature for 1 hour and the solvents were removed in vacuo. Dry toluene was added and removed in vacuo.

The resulting acid chloride was dissolved in dry THF. Aniline (1.1 equivalents) and of triethylamine (2 equivalents) were added to the reaction mixture at 0-5 °C and stirred for further one hour at 0 °C. The solvent was removed *in vacuo* and the crude product was chromatographed (silica EtOAc-hexanes) to give the desired substituted phenyl-*N*-benzamide.

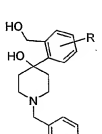
Substituted 10-benzylspiro[3-hydroisobenzofuran-3,4'-piperidine]-1-one:



A solution of the substituted phenyl-*N*-benzamide in dry THF was cooled to -10 °C and 2 quivalents of *n*-BuLi (1.6 M) in hexanes were added over 2 hours. The reaction mixture was stirred for 30 minutes and 1-benzyl-4-piperidone (1.1 equivalents) was added over 15 minutes. The reaction mixture was stirred at room temperature for further 45 minutes.

The reaction mixture was poured over saturated NH_4Cl, extracted with ether (x3) and the combined ether extracts were washed with brine and subsequently extracted with 2N HCl solution. The combined HCl extracts were cooled to yield the desired HCl salt of the amine. The free base was liberated by addition of NH_4OH and the free base was extracted with ethyl acetate (x3). The combined ethyl acetate extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the desired substituted 10-benzylspiro[3-hydroisobenzofuran-3,4'-piperidine]-1-one.

Substituted 1-Benzyl-4-(2-hydroxymethyl-phenyl)-piperidin-4-ol:

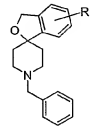


A mixture of 1 equivalent of substituted 10-benzylspiro[3-hydroisobenzofuran-3,4'-piperidine]-1-one and 1.3

equivalents of LAH in THF (1M) was heated at reflux temperature for one hour. The excess LAH was then quenched by the sequential addition of one weight equivalent of water, one weight equivalent of 2N NaOH solution and 3 weight equivalents of water, as described in Fieser and Fieser (Reagents for Organic Synthesis, Vol. 1).

The reaction mixture was filtered and the filter cake was washed with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo* to give the desired substituted 1-benzyl-4-(2-hydroxymethyl-phenyl)-piperidin-4-ol.

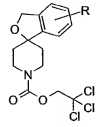
10-Benzylspiro[1,3-dihydroisobenzofuran-1,4'-piperidine]:



A mixture of substituted 1-benzyl-4-(2-hydroxymethyl-phenyl)-piperidin-4-ol (1 equivalent) and triethyl amine (2.5 equivalents) in THF-toluene was treated with methanesulfonyl chloride (1.2 equivalents) at room temperature (exotherm to ca. 35 °C).

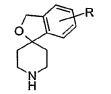
The reaction mixture was stirred for 1 hour, poured into water, separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude product was chromatographed (silica, ethyl acetate-hexane) to give the desired benzyl protected spirocyclic piperidine.

Substituted 2,2,2-Trichloroethyl Spiro[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-carboxylate:



To a solution of benzyl amine in dichloroethane was added 2,2,2-trichloroethylchloroformate (3 equivalents) and the resulting mixture was heated at reflux temperature for 1 hour. The solvent was removed *in vacuo*, water was added to the reaction mixture and extracted with ethyl acetate (x3). The combined ethyl acetate extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude product was chromatographed (silica, ethyl acetate-hexane) to give the desired carbamate.

Substituted Spiro[1,3-dihydroisobenzofuran-1,4'-piperidine]



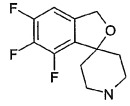
The substituted 2,2,2-Trichloroethyl spiro[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-carboxylate (0.071 mole) in 400 mL of acetic acid was heated to 40 °C and zinc powder was added over one hour. The resulting mixture was heated at 40 °C overnight, cooled to room temperature, filtered, cooled in an ice-bath and neutralized by addition of NH_4OH.

The resulting mixture was extracted with ethyl acetate (x3), the combined ethyl acetate extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed *in vacuo*.

The crude product was chromatographed (silica, ethyl acetate-hexane) to give the desired spirocyclic piperidine.

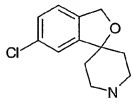
The hydrochlorides were prepared by addition of HCl in ether (1N) to the free base in ethyl acetate.

4,5,6-TRIFLUOROSPIRO[1,3-DIHYDROISOBENZOFURAN-3,4'-PIPERIDINE]:



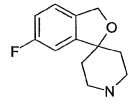
^{1}H NMR (400 MHz, MeOD) δ 7.11-7.01 (m, 1H), 5.06 (s, 2H), 3.08-2.94 (m, 4H), 2.31 (dt, 2H, J = 5.5, 13.0 Hz), 1.79 (d, 2H, J = 14.0 Hz).

5-CHLOROSPIRO[1,3-DIHYDROISOBENZOFURAN-3,4'-PIPERIDINE]:



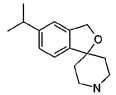
^{1}H NMR (400 MHz, MeOD) δ 7.33-7.28 (m, 1H), 7.27-7.23 (m, 2H), 5.04 (s, 2H), 3.13-3.03 (m, 4H), 1.97-1.87 (m, 2H), 1.80-1.72 (m, 2H).

5-FLUOROSPIRO[1,3-DIHYDROISOBENZOFURAN-3,4'-PIPERIDINE]:



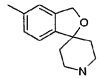
^{1}H NMR (400 MHz, MeOD) δ 7.28-7.22 (m, 1H), 7.06-6.94 (m, 2H), 5.03 (s, 2H), 3.10-2.98 (m, 4H), 1.94-1.84 (m, 2H), 1.78-1.69 (m, 2H).

5-(METHYLETHYL)SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE] HYDROCHLORIDE:



^{1}H NMR (400 MHz, MeOD) δ 7.26-7.19 (m, 2H), 7.11 (s, 1H), 5.08 (s, 2H), 3.47-3.37 (m, 4H), 3.02-2.93 (m, 1H), 2.25-2.14 (m, 2H), 1.97-1.89 (m, 2H), 1.28 (d, 6H, J = 6.4 Hz).

5-METHYLSPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE] HYDROCHLORIDE:



^{1}H NMR (400 MHz, MeOD) δ 7.19-7.08 (m, 3H), 5.07 (s, 2H), 3.46-3.31 (m, 4H), 2.38 (s, 3H), 2.23-2.12 (m, 2H), 1.96-1.88 (m, 2H).

Synthesis and Analysis of Specific Compounds

Example 1

2-(4-(-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)BUTYL) BENZO[C]AZOLINE-1,3-DIONE:

Example 1 was prepared from spiro[indene-1,4'-piperidine] and 2-(4-bromobutYLBenzo[c]azoline-1,3-dione according to the procedures described in Scheme H: ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.77 (m, 2H), 7.73-7.65 (m, 2H), 7.41-7.26 (m, 2H), 7.25-7.14 (m, 2H), 6.83 (d, 1H, J = 5.8 Hz), 6.73 (d, 1H, J = 5.8 Hz), 3.74 (t, 2H, J = 6.8 Hz), 3.01 (d, 2H, J = 11.6 Hz), 2.58-2.47 (m, 2H), 2.34 (t, 2H, J = 11.8 Hz), 2.20 (t, 2H, J = 12.6 Hz), 1.83-1.71 (m, 2H), 1.69-1.57 (m, 2H), 1.34 (d, 2H, J = 12.8 Hz); ESMS m/e: 387.2 $(M + H)^+$.

Example 2

(4-PHENYL)PHENYL)-N-(6-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)HEXYL)CARBOXAMIDE:

Example 2 was prepared from 6-(SPIRO[indane-1,4'-piperidine]-10-YL)HEXYLamine and 4-phenylbenzoyl chloride according to the procedures described in Scheme F: ESMS m/e: 467.2 $(M + H)^+$.

Example 3

2,2-DIPHENYL-N-(5-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PENTYL)ACETAMIDE:

Example 3 was prepared from (5-(SPIRO[indane-1,4'-piperidine]-10-yl)pentyl)amine and 2,2-diphenylacetyl chloride according to the procedures described in Scheme F: ESMS m/e: 467.2 $(M + H)^+$.

Example 4

2,2-DIPHENYL-N-(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)ACETAMIDE:

Example 4 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and 2,2-diphenylacetyl chloride according to the procedures described in Scheme F: ESMS m/e: 453.2 $(M + H)^+$.

Example 5

2,2-DIPHENYL-N-(6-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-Y)LHEXYL)ACETAMIDE:

Example 5 was prepared from 6-(SPIRO[indane-1,4'-piperidine]-10-YL)HEXYLamine and 2,2-diphenylacetyl chloride according to the procedures described in Scheme F: ESMS m/e: 481.2 $(M + H)^+$.

Example 6

2,2-DIPHENYL-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 6 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 2,2-diphenylacetyl chloride according to the procedures described in Scheme F: ESMS m/e: 439.2 $(M + H)^+$.

Example 7

(3,5-DICHLOROPHENYL)-N-[(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)AMINO]CARBOXAMIDE:

Example 7 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and 3,5-dichlorobenzoyl chloride according to the procedures described in Scheme G: ESMS m/e: 431.1 $(M + H)^+$.

Example 8

(3,5-DICHLOROPHENYL)-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 8 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 3,5-dichlorobenzoyl chloride according to the procedures described in Scheme F: ESMS m/e: 417.1 $(M + H)^+$.

Example 9

2-(4-FLUOROPHENYL)-N-(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)ACETAMIDE:

Example 9 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and 2-(4-fluorophenyl)acetyl chloride according to the procedures described in Scheme F: ESMS m/e: 395.2 $(M + H)^+$.

Example 10

[1-(4-CHLOROPHENYL)-3-PROPYL)PYRAZOL-4-YL]-N-(6-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)HEXYL)CARBOXAMIDE:

Example 10 was prepared from 6-(SPIRO[indane-1,4'-piperidine]-10-YL)HEXYLamine and 1-(4-chlorophenyl)-3-propyl)pyrazole-4-carbonyl chloride according to the procedures described in Scheme F: ESMS m/e: 533.2 $(M + H)^+$.

Example 11

[3-(2-CHLORO-6-FLUOROPHENYL)-5-METHYLISOXAZOL-4-YL]-N-(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)CARBOXAMIDE:

Example 11 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and 3-(2-chlorophenyl)-5-methylisoxazole-4-carbonyl chloride according to the procedures described in Scheme F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.45 (m, 1H), 7.41-7.37 (m, 1H), 7.23-7.15 (m, 5H), 5.42 (s, 1H), 3.26 (dd, 2H, J = 6.2, 12.2 Hz), 2.89 (t, 2H, J = 7.2 Hz), 2.86-2.79 (m, 2H), 2.78 (s, 3H), 2.31 (t, 2H, J = 7.2 Hz), 2.15-2.05 (m, 2H), 1.99 (t, 2H, J = 7.2 Hz), 1.96-1.86 (m, 2H), 1.58-1.50 (m, 2H), 1.43-1.34 (m, 4H); ESMS m/e: 496.2 $(M + H)^+$.

Example 12

[3-(2-CHLORO-6-FLUOROPHENYL)-5-METHYLISOXAZOL-4-YL]-N-(6-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)HEXYL)CARBOXAMIDE:

Example 12 was prepared from 6-(SPIRO[indane-1,4'-piperidine]-10-YL)HEXYLamine and 3-(2-chloro-6-

fluorophenyl)-5-methylisoxazole-4-carbonyl chloride according to the procedures described in Scheme F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.47 (m, 1H), 7.42-7.38 (m, 1H), 7.23-7.13 (m, 5H), 5.19 (s, 1H), 3.22 (dd, 2H, J = 6.8, 12.5 Hz), 2.89 (t, 4H, J = 7.2 Hz), 2.78 (s, 3H), 2.37-2.31 (m, 2H), 2.19-2.09 (m, 2H), 2.03-1.98 (m, 4H), 1.59-1.52 (m, 4H), 1.36-1.28 (m, 2H), 1.27-1.20 (m, 2H), 1.17-1.09 (m, 2H); ESMS m/e: 524.2 $(M + H)^+$.

Example 13

(3,5-DIFLUOROPHENYL)-N-(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)CARBOXAMIDE:

Example 13 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and 3,5-difluorobenzoyl chloride according to the procedures described in Scheme F: ESMS m/e: 399.2 $(M + H)^+$.

Example 14

[5-(3,5-dichlorophenoxy)(2-furyl)]-N-(4-(spiro[indane-1,4'-piperidine]-10-yl)butyl)carboxamide:

Example 14 was prepared from 6-(SPIRO[indane-1,4'-piperidine]-10-YL)HEXYLamine and 3,5-difluorobenzoyl chloride according to the procedures described in Scheme F: ESMS m/e: 427.2 $(M + H)^+$.

Example 15

[5-(3,5-dichlorophenoxy)(2-furyl)]-N-(4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)carboxamide:

Example 15 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and 5-(3,5-dichlorophenoxy)furan-2-carbonyl chloride according to the procedures described in Scheme F: ESMS m/e: 513.1 $(M + H)^+$.

Example 16

[5-(3,5-DICHLOROPHENOXY)(2-FURYL)]-N-(6-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)HEXYL)CARBOXAMIDE:

Example 16 was prepared from 6-(SPIRO[indane-1,4'-piperidine]-10-YL)HEXYLamine and 5-(3,5-dichlorophenoxy)furan-2-carbonyl chloride according to the procedures described in Scheme F: ESMS m/e: 541.2 $(M + H)^+$.

Example 17

[5-(3,5-DICHLOROPHENOXY)(2-FURYL)]-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 17 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 5-(3,5-dichlorophenoxy)furan-2-carbonyl chloride according to the procedures described in Scheme F: ESMS m/e: 499.1 $(M + H)^+$.

Example 18

(3-CHLOROPHENYL)-N-(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)CARBOXAMIDE:

Example 18 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and 3-chlorobenzoyl chloride according to the procedures described in Scheme F: ESMS m/e: 397.1 $(M + H)^+$.

Example 19

(3,4-DIFLUOROPHENYL)-N-(6-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)HEXYL)CARBOXAMIDE:

Example 19 was prepared from 6-(SPIRO[indane-1,4'-piperidine]-10-YL)HEXYLamine and 3,4-difluorobenzoyl chloride according to the procedures described in Scheme F: ESMS m/e: 427.2 $(M + H)^+$.

Example 20

[3-(TERT-BUTYL)-1-BENZYL)PYRAZOL-5-YL]-N-(6-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)HEXYL)CARBOXAMIDE:

Example 20 was prepared from 6-(SPIRO[indane-1,4'-piperidine]-10-YL)HEXYLamine and 3-(tert-butyl)-1-benzyl)pyrazole-5-carbonyl chloride according to the procedures described in Scheme F: ESMS m/e: 527.3 $(M + H)^+$.

Example 21

(5-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PENTYL){[3-(TRIFLUORO-METHYL)PHENYL]SULFONYL}AMINE:

Example 21 was prepared from 5-(SPIRO[indane-1,4'-piperidine]-10-yl)pentylamine and chloro[3-(trifluoromethyl)phenyl]sulfone according to the procedures described in Scheme F: ESMS m/e: 481.2 $(M+H)^+$.

Example 22

(NAPHTHYLAMINO)[(5-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PENTYL)AMINO]METHANE-1-THIONE:

Example 23 was prepared from 5-(SPIRO[indane-1,4'-piperidine]-10-yl)pentylamine and naphthalenisothiocyanate according to the procedures described in Scheme G: ESMS m/e: 458.2 $(M + H)^+$.

Example 23

(NAPHTHYLAMINO)[(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL-BUTYL)AMINO]METHANE-1-THIONE:

Example 22 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and naphthalenisothiocyanate according to the procedures described in Scheme G: ESMS m/e: 444.2 $(M + H)^+$.

Example 24

(NAPHTHYLAMINO)[(6-SPIRO[INDANE-1,4'-PIPERIDINE]-10-YLHEXYL)AMINO] METHANE-1-THIONE:

Example 24 was prepared from 6-spiro[indane-1,4'-piperidine]-10-ylhexylamine and naphthalenisothiocyanate according to the procedures described in Scheme G: ESMS m/e: 472.2 $(M + H)^+$.

Example 25

N-(3,5-DICHLOROPHENYL)[(5-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PENTYL)AMINO]CARBOXAMIDE:

Example 25 was prepared from 5-(SPIRO[indane-1,4'-piperidine]-10-yl)pentylamine and 3,5-dichlorobenzenisocyanate according to the procedures described in Scheme G: ESMS m/e: 460.1 $(M + H)^+$.

Example 26

N-(3,5-DICHLOROPHENYL)[(4-SPIRO[INDANE-1,4'-PIPERIDINE]-10-YLBUTYL)AMINO] CARBOXAMIDE:

Example 26 was prepared from (4-spiro[indane-1,4'-piperidine]-10-ylbutyl)amine and 3,5-dichlorobenzenisocyanate according to the procedures described in Scheme G: ESMS m/e: 446.1 $(M + H)^+$.

Example 27

N-(4-PHENYL)PHENYL)[(5-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PENTYL)AMINO]CARBOXAMIDE:

Example 27 was prepared from 5-(SPIRO[indane-1,4'-piperidine]-10-YL)PENTYLamine and 4-phenylbenzenisocyanate according to the procedures described in Scheme G: ESMS m/e: 468.3 $(M + H)^+$.

Example 28

N-(4-PHENYL)PHENYL)[(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)AMINO]CARBOXAMIDE:

Example 28 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and 4-phenylbenzenisocyanate according to the procedures described in Scheme G: ESMS m/e: 454.2 $(M + H)^+$.

Example 29

(4-PHENYL)PHENYL)-N-(6-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)HEXYL)CARBOXAMIDE:

Example 29 was prepared from 6-(SPIRO[indane-1,4'-piperidine]-10-YL)HEXYLamine and 4-phenylbenzenisocyanate according to the procedures described in Scheme G: ESMS m/e: 467.2 $(M + H)^+$.

Example 30

(5-METHYL-3-PHENYLISOXAZOL-4-YL)-N-(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)CARBOXAMIDE:

Example 30 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and 5-methyl-3-phenylisoxazole-4-carbonyl chloride according to the procedures described in Scheme F: ESMS m/e: 444.2 $(M + H)^+$.

Example 31

[2-(4-CHLOROPHENOXY)(3-PYRIDYL)]-N-(5-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PENTYL)CARBOXAMIDE:

Example 31 was prepared from (5-(SPIRO[indane-1,4'-piperidine]-10-YL)PENTYL)amine and 2-(4-chlorophenoxy)pyridine-3-carbonyl chloride according to the procedures described in Scheme F: ESMS m/e: 504.1 $(M + H)^+$.

Example 32

[2-(4-CHLOROPHENOXY)(3-PYRIDYL)]-N-(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)CARBOXAMIDE:

Example 32 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and 2-(4-chlorophenoxy)pyridine-3-carbonyl chloride according to the procedures described in Scheme F: ESMS m/e: 490.1 $(M + H)^+$.

Example 33

[2-(4-CHLOROPHENOXY)(3-PYRIDYL)]-N-(6-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)HEXYL)CARBOXAMIDE:

Example 33 was prepared from (6-(SPIRO[indane-1,4'-piperidine]-10-YL)HEXYL)amine and 2-(4-chlorophenoxy)pyridine-3-carbonyl chloride according to the procedures described in Scheme F: ESMS m/e: 518.2 $(M + H)^+$.

Example 34

(3-CHLOROBENZO[B]THIOPHEN-2-YL)-N-(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)CARBOXAMIDE:

Example 34 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL) amine and 3-chlorobenzo[b]thiophene-2-carbonyl chloride according to the procedures described in Scheme F: ESMS m/e: 453.1 $(M + H)^+$.

Example 35

[3-(2-CHLOROPHENYL)-5-METHYLISOXAZOL-4-YL]-N-(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)CARBOXAMIDE:

Example 35 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL) amine and 3-(2-chlorophenyl)-5-methylisoxazole-4-carbonyl chloride according to the procedures described in Scheme F: ESMS m/e: 478.1 $(M + H)^+$.

Example 36

(3-CHLOROBENZO[B]THIOPHEN-2-YL)-N-(5-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PENTYL)CARBOXAMIDE:

Example 36 was prepared from 5-(SPIRO[indene-1,4'-piperidine]-10-yl)pentylamine and 3-chlorobenzo[b]thiophene-2-carbonyl chloride according to the procedures described in Scheme F: ^1H NMR (400 MHz, $CDCl_3$) δ 7.90-7.82 (m, 2H), 7.52-7.47 (m, 2H), 7.38 (d, 1H, J = 7.3 Hz), 7.31 (d, 1H, J = 7.3 Hz), 7.24-7.15 (m, 3H), 6.83 (d, 1H, J = 6.0 Hz), 6.75 (d, 1H, J = 5.6 Hz), 3.60-3.52 (m, 2H), 3.09 (d, 2H, J = 11.2 Hz), 2.56 (t, 2H, J = 7.6 Hz), 2.41 (t, 2H, J = 11.8 Hz), 2.28 (t, 2H, J = 11.8 Hz), 1.80-1.65 (m, 4H), 1.55-1.45 (m, 2H), 1.38 (d, 2H, J = 12.4 Hz); ESMS m/e: 465.0 $(M + H)^+$.

Example 37

[3-(TERT-BUTYL)-1-BENZYL)PYRAZOL-5-YL]-N-(5-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PENTYL)CARBOXAMIDE:

Example 37 was prepared from 5-(SPIRO[indene-1,4'-piperidine]-10-yl)pentylamine and 3-(tert-butyl)-1-benzyl)pyrazole-5-carbonyl chloride according to the procedures described in Scheme F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.15 (m, 9H), 6.79 (dd, 2H, J = 5.8, 18.2 Hz), 6.39 (s, 1H), 6.07 (s, 1H), 5.72 (s, 2H), 3.40-3.30 (m, 2H), 3.15-3.07 (m, 2H), 2.53 (t, 2H, J = 7.6 Hz), 2.47-2.35 (m, 2H), 2.35-2.23 (m, 2H), 1.70-1.52 (m, 4H), 1.44-1.34 (m, 4H), 1.32 (s, 9H); ESMS m/e: 511.3 $(M + H)^+$.

Example 38

2,2-DIPHENYL-N-(3-SPIRO[INDENE-1,4'-PIPERIDINE]-10-YLPROPYL)ACETAMIDE:

Example 38 was prepared from 3-spiro[indene-1,4'-piperidine]-10-ylpropylamine and 2,2-diphenylacetyl chloride according to the procedures described in Scheme F: ESMS m/e: 437.2 $(M + H)^+$.

Example 39

2,2-DIPHENYL-N-(3-SPIRO[1,2,3,4-TETRAHYDRONAPHTHALENE-1,4'-PIPERIDINE]-11-YLPROPYL)ACETAMIDE:

Example 39 was prepared from 3-spiro[1,2,3,4-tetrahydronaphthalene-1,4'-piperidine]-11-ylpropylamine and 2,2-diphenylacetic acid according to the procedures described in Scheme F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.00 (m, 15H), 4.87 (s, 1H), 3.36 (dd, 2H, J = 5.6, 12.0 Hz), 2.91 (d, 2H, J = 7.2 Hz), 2.75 (t, 2H, J = 6.0 Hz), 2.59 (t, 2H, J = 6.8 Hz), 2.37 (t, 2H, J = 12.0 Hz), 2.18 (dt, 2H, J = 3.6, 13.8 Hz), 1.86-1.66 (m, 6H), 1.59 (d, 2H, J = 14.0 Hz); ESMS m/e: 453.4 $(M + H)^+$.

Example 40

2,2-DIPHENYL-N-(5-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PENTYL)ACETAMIDE:

Example 40 was prepared from 5-(SPIRO[indene-1,4'-piperidine]-10-yl)pentylamine and 2,2-diphenylacetyl

chloride according to the procedures described in Scheme H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.10 (m, 14H), 6.83 (d, 1H, J = 5.6 Hz), 6.74 (d, 1H, J = 5.6 Hz), 5.73 (s, 1H), 4.92 (s, 1H), 3.34-3.23 (m, 2H), 3.06-2.85 (m, 4H), 2.48-2.14 (m, 4H), 2.03-1.94 (m, 2H), 1.62-1.45 (m, 4H), 1.40-1.25 (m, 2H); ESMS m/e: 465.1 $(M + H)^+$.

Example 41

2,2-DIPHENYL-N-(2-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YLETHYL) ACETAMIDE: Example 41 was prepared from 2-(SPIRO[indane-1,4'-piperidine]-10-ylethylamine and 2,2-diphenylacetyl chloride according to the procedures described in Scheme F:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.10 (m, 14H), 6.41 (br, 1H), 4.99 (s, 1H), 3.40 (dd, 2H, J = 5.8, 11.0 Hz), 2.95-2.81 (m, 4H), 2.73-2.65 (m, 2H), 2.48 (t, 2H, J = 6.0 Hz), 2.14 (dt, 2H, J = 2.4, 11.8 Hz), 1.95 (t, 2H, J = 7.4 Hz), 1.48-1.40 (m, 2H); ESMS m/e: 425.2 $(M + H)^+$.

Example 42

NAPHTHYL-N-(2-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YLETHYL) CARBOXAMIDE:

Example 42 was prepared from 2-(SPIRO[indane-1,4'-piperidine]-10-ylethylamine and naphthalenecarbonyl chloride according to the procedures described in Scheme F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39-8.35 (m, 1H), 7.96-7.87 (m, 2H), 7.67 (dd, 1H, J = 1.2, 5.4 Hz), 7.59-7.47 (m, 3H), 7.25-7.11 (m, 4H), 6.70 (s, 1H), 3.69 (dd, 2H, J = 5.1, 11.4 Hz), 2.97-2.85 (m, 4H), 2.69 (t, 2H, J = 6.3 Hz), 2.27 (dt, 2H, J = 2.4, 12.0 Hz), 2.02 (t, 2H, J = 7.5 Hz), 1.89 (dt, 2H, J = 4.1, 13.0 Hz), 1.58-1.50 (m, 2H); ESMS m/e: 385.2 $(M + H)^+$.

Example 43

(3-CHLOROPHENYL)-N-(2-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YLETHYL) CARBOXAMIDE:

Example 43 was prepared from 2-(SPIRO[indane-1,4'-piperidine]-10-ylethylamine and 3-chlorobenzoyl chloride according to the procedures described in Scheme F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.78 (m, 1H), 7.79-7.66 (m, 1H), 7.51-7.46 (m, 1H), 7.40 (t, 1H, J = 7.8 Hz), 7.22-7.12 (m, 4H), 7.02 (s, 1H), 3.62-3.55 (m, 2H), 2.97-2.83 (m, 4H), 2.67 (t, 2H, J = 5.8 Hz), 2.28 (dt, 2H, J = 2.2, 12.2 Hz), 2.03 (t, 2H, J = 7.4 Hz), 1.94 (dt, 2H, J = 3.8, 13.0 Hz), 1.65-1.50 (m, 2H); ESMS m/e: 369.1 $(M + H)^+$.

Example 44

(3,5-DICHLOROPHENYL)-N-(2-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YLETHYL)CARBOXAMIDE:

Example 44 was prepared from 2-(SPIRO[indane-1,4'-piperidine]-10-ylethylamine and 3,5-dichlorobenzoyl chloride according to the procedures described in Scheme F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, 1H, J = 1.8 Hz), 7.50 (t, 1H, J = 2.0 Hz), 7.24-7.14 (m, 5H), 7.05 (br, 1H), 3.61-3.54 (m, 2H), 3.00-2.85 (m, 4H), 2.68 (t, 2H, J = 6.0 Hz), 2.30 (t, 2H, J = 11.6 Hz), 2.10-1.90 (m, 4H), 1.59 (d, 2H, J = 12.4 Hz); ESMS m/e: 403.1 $(M + H)^+$.

Example 45

(3,4-DIFLUOROPHENYL)-N-(2-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YLETHYL)CARBOXAMIDE:

Example 45 was prepared from 2-(SPIRO[indane-1,4'-piperidine]-10-ylethylamine and 3,4-difluorobenzoyl chloride according to the procedures described in Scheme F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.66 (m, 1H), 7.60-7.54 (m, 1H), 7.22-7.14 (m, 5H), 7.01 (s, 1H), 3.62-3.52 (m, 2H), 2.97-2.82 (m, 4H), 2.67 (t, 2H, J = 6.0 Hz), 2.29 (dt, 2H, J = 2.0, 12.0 Hz), 2.03 (t, 2H, J = 7.3 Hz), 1.94 (dt, 2H, J = 3.6, 13.2 Hz), 1.62-1.56 (m, 2H); ESMS m/e: 371.1 $(M + H)^+$.

Example 47

2,2-DIPHENYL-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)PROPANAMIDE:

Example 47 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 2,2-diphenyl)propanoic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.07 (m, 14H), 6.29 (s, 1H), 3.36 (dd, 2H, J = 6.0, 12.4 Hz), 2.87 (t, 2H, J = 7.6 Hz), 2.75 (d, 2H, J = 11.6 Hz), 2.32 (t, 2H, J = 6.8 Hz), 2.10-2.00 (m, 2H), 2.01 (s, 3H), 1.96 (t, 2H, J = 7.2 Hz), 1.80-1.70 (m, 2H), 1.69 (t, 2H, J = 6.4 Hz), 1.45 (d, 2H, J = 12.8 Hz); ESMS m/e: 453.3 $(M + H)^+$.

Example 48

2,2-BIS(4-METHYL)PHENYL)-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 48 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 2,2-bis(4-methyl)phenyl)acetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.08 (m, 12H), 6.90 (s, 1H), 4.82 (s, 1H), 3.42-3.34 (m, 2H), 2.94-2.75 (m, 4H), 2.41 (t, 2H, J = 6.8 Hz), 2.29 (s, 6H), 2.15-2.04 (m, 2H), 2.01-1.93 (m, 2H), 1.82 (dt, 2H, J = 3.6, 13.2 Hz), 1.75-1.65 (m, 2H), 1.50 (dd, 2H, J = 2.6, 12.8 Hz); ESMS m/e: 467.3 $(M + H)^+$.

Example 49

2,2,2-TRIPHENYL-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 49 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 2,2,2-triphenylacetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.06 (m, 19H), 6.28 (s, 1H), 3.42 (dd, 2H, J = 6.4, 12.4 Hz), 2.87 (t, 2H, J = 6.8 Hz), 2.78-2.68 (m, 2H), 2.31 (t, 2H, J = 7.0 Hz), 2.11-1.98 (m,

2H), 1.95 (t, 2H, J = 7.4 Hz), 1.81-1.59 (m, 4H), 1.44 (d, 2H, J = 12.4 Hz); ESMS m/e: 515.3 $(M + H)^+$.

Example 50

2-(4-CHLOROPHENYL)-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)PROPANAMIDE:

Example 50 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 2-(4-chlorophenyl)propanoic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.14 (m, 8H), 6.97 (s, 1H), 3.51 (q, 1H, J = 7.3 Hz), 3.39-3.26 (m, 2H), 2.94-2.75 (m, 4H), 2.41 (dt, 2H, J = 1.2, 6.8 Hz), 2.16-2.06 (m, 2H), 2.19 (t, 2H, J = 7.4 Hz), 1.92-1.78 (m, 2H), 1.72-1.62 (m, 2H), 1.61-1.53 (m, 2H), 1.51 (d, 3H, 7.4 Hz); ESMS m/e: 411.3 $(M + H)^+$.

Example 51

[1-(4-CHLOROPHENYL)-2-METHYL-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)PROPANAMIDE:

Example 51 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 2-(4-chlorophenyl)-2-methyl)propanoic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.25 (m, 4H), 7.24-7.10 (m, 4H), 6.62 (s, 1H), 3.32 (dd, 2H, J = 6.2, 11.6 Hz), 2.89 (t, 2H, J = 7.4 Hz), 2.83-2.72 (m, 2H), 2.37 (t, 2H, J = 6.4 Hz), 2.12-2.02 (m, 2H), 1.97 (t, 2H, J = 7.2 Hz), 1.77 (dt, 2H, J = 3.6, 12.8 Hz), 1.70-1.61 (m, 2H), 1.59 (s, 6H), 1.52-1.44 (m, 2H); ESMS m/e: 425.3 $(M + H)^+$.

Example 52

[1-(4-CHLOROPHENYL)CYCLOPENTYL]-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 52 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 1-(4-chlorophenyl)cyclopentanecarboxylic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ

7.36-7.13 (m, 8H), 6.62 (s, 1H), 3.27 (dd, 2H, J = 5.6, 12.0 Hz), 2.90 (t, 2H, J = 7.2 Hz), 2.85-2.75 (m, 2H), 2.57-2.47 (m, 2H), 2.34 (t, 2H, J = 6.4 Hz), 2.12-2.02 (m, 2H), 2.02-1.92 (m, 4H), 1.92-1.68 (m, 6H), 1.68-1.59 (m, 2H), 1.56-1.48 (m, 2H); ESMS m/e: 451.3 $(M + H)^+$.

Example 53

1-[(4-CHLOROPHENYL)CYCLOHEXYL]-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 53 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 1-(4-chlorophenyl)cyclohexanecarboxylic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.11 (m, 8H), 6.94 (s, 1H), 3.30 (dd, 2H, J = 6.0, 12.0 Hz), 2.93-2.75 (m, 4H), 2.40-2.30 (m, 4H), 2.12-2.02 (m, 2H), 1.98 (t, 2H, J = 7.2 Hz), 1.95-1.80 (m, 5H), 1.68-1.56 (m, 7H), 1.56-1.50 (m, 2H); ESMS m/e: 465.3 $(M + H)^+$.

Example 54

[(4-FLUOROPHENYL)CYCLOPENTYL]-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 54 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 1-(4-fluorophenyl)cyclopentanecarboxylic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (m, 2H), 7.24-7.13 (m, 4H), 7.04-6.95 (m, 2H), 6.59 (s, 1H), 3.28 (dd, 2H, J = 5.6, 12.0 Hz), 2.90 (t, 2H, J = 7.4 Hz), 2.85-2.75 (m, 2H), 2.58-2.48 (m, 2H), 2.34 (t, 2H, J = 6.4 Hz), 2.12-2.02 (m, 2H), 2.02-1.92 (m, 4H), 1.92-1.68 (m, 6H), 1.67-1.58 (m, 2H), 1.56-1.47 (m, 2H); ESMS m/e: 435.3 $(M + H)^+$.

Example 55

2,2-BIS(4-CHLOROPHENYL)-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 55 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 2,2-bis(4-chlorophenyl)acetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.32-7.10 (m, 12H), 4.77 (s, 1H), 3.41 (dd, 2H, J = 5.6, 11.6 Hz), 2.93-2.78 (m, 4H), 2.46 (t, 2H, J = 6.4 Hz), 2.13 (dt, 2H, J = 2.0, 12.0 Hz), 1.99 (t, 2H, J = 7.2 Hz), 1.80 (dt, 2H, J = 3.6, 13.2 Hz), 1.74-1.66 (m, 2H), 1.53 (d, 2H, J = 12.8 Hz); ESMS m/e: 507.2 $(M + H)^+$.

Example 56

[1-(4-FLUOROPHENYL)CYCLOHEXYL]-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 56 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamin and 1-(4-fluorophenyl)cyclohexanecarboxylic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.38 (m, 2H), 7.25-7.12 (m, 4H), 7.04-6.96 (m, 2H), 6.91 (s, 1H), 3.30 (dd, 2H, J = 6.0, 12.0 Hz), 2.70 (t, 2H, J = 7.2 Hz), 2.84-2.77 (m, 2H), 2.41-2.32 (m, 4H), 2.11-2.01 (m, 2H), 1.98 (t, 2H, J = 7.2 Hz), 1.95-1.80 (m, 5H), 1.68-1.56 (m, 7H), 1.56-1.48 (m, 2H); ESMS m/e: 449.4 $(M + H)^+$.

Example 57

2,2-BIS(4-FLUOROPHENYL)-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 57 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 2,2-bis(4-fluorophenyl)acetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.31-7.11 (m, 8H), 7.05-6.96 (m, 4H), 4.80 (s, 1H), 3.41 (dd, 2H, J = 6.0, 11.6 Hz), 2.93-2.78 (m, 4H), 2.45 (t, 2H, J = 6.4 Hz), 2.12 (dt, 2H, J = 2.0, 12.0 Hz), 1.99 (t, 2H, J = 7.4 Hz), 1.80 (dt, 2H, J = 4.0, 12.8 Hz),

1.75-1.66 (m, 2H), 1.58-1.48 (m, 2H); ESMS m/e: 475.3 (M + H)$^+$.

Example 58

[1-(4-CHLOROPHENYL)CYCLOPROPYL]-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 58 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 1-(4-chlorophenyl)cyclopropanecarboxylic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.32 (m, 4H), 7.24-7.11 (m, 4H), 5.61 (s, 1H), 3.25 (dd, 2H, J = 6.6, 13.0 Hz), 2.88 (t, 2H, J = 7.2 Hz), 2.80-2.70 (m, 2H), 2.31 (t, 2H, J = 7.2 Hz), 2.14-2.03 (m, 2H), 1.97 (t, 2H, J = 7.4 Hz), 1.83 (dt, 2H, J = 4.0, 13.2 Hz), 1.68-1.55 (m, 4H), 1.52-1.45 (m, 2H), 1.01 (dd, 2H, J = 3.6, 6.8 Hz); ESMS m/e: 423.3 (M + H)$^+$.

Example 59

[1-(4-CHLOROPHENYL)CYCLOBUTYL]-N-(3-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 59 was prepared from 3-(SPIRO[indane-1,4'-piperidine]-10-yl)propylamine and 1-(4-chlorophenyl)cyclobutanecarboxylic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.10 (m, 8H), 6.57 (s, 1H), 3.29 (dd, 2H, J = 5.8, 11.8 Hz), 2.95-2.75 (m, 6H), 2.52-2.40 (m, 2H), 2.35 (t, 2H, J = 6.4 Hz), 2.16-1.80 (m, 8H), 1.70-1.60 (m, 2H), 1.58-1.50 (m, 2H); ESMS m/e: 437.3 (M + H)$^+$.

Example 60

(3,4-DIFLUOROPHENYL)-N-(4-(SPIRO[INDANE-1,4'-PIPERIDINE]-10-YL)BUTYL)CARBOXAMIDE:

Example 60 was prepared from (4-(SPIRO[indane-1,4'-piperidine]-10-YL)BUTYL)amine and 3,4-difluorobenzoyl chloride according to the procedures described in Scheme F: ESMS m/e: 399.0 (M + H)$^+$.

Example 61

2,2-DIPHENYL-N-(3-(SPIRO[INDANE-2,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 61 was prepared from spiro[indane-2,4'-piperidine] and N-(3-bromopropyl)-2,2-diphenylacetamide according to the procedures described in Scheme H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.12 (m, 14H), 7.04 (s, 1H), 4.89 (s, 1H), 3.40 (dd, 2H, J = 5.8, 12.2 Hz), 2.89 (t, 2H, J = 7.0 Hz), 2.84-2.77 (m, 2H), 2.41 (t, 2H, J = 6.6 Hz), 2.09 (dt, 2H, J = 2.2, 12.4 Hz), 1.98 (t, 2H, J = 7.2 Hz), 1.80 (dt, 2H, J = 4.0, 13.2 Hz), 1.75-1.66 (m, 2H), 1.54-1.46 (m, 2H); ESMS m/e: 439.3 $(M + H)^+$.

Example 62

2,2-BIS(4-METHYL)PHENYL)-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 62 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 2,2-bis(4-methyl)phenyl)acetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.05 (m, 13H), 6.79 (d, 1H, J = 5.6 Hz), 6.75 (d, 1H, J = 5.6 Hz), 4.85 (s, 1H), 3.45-3.35 (m, 2H), 2.99-2.80 (m, 2H), 2.55-2.40 (m, 2H), 2.40-2.20 (m, 2H), 2.29 (s, 6H), 2.15-1.90 (m, 2H), 1.80-1.65 (m, 2H), 1.31 (d, 2H, J = 13.2 Hz); ESMS m/e: 465.3 $(M + H)^+$.

Example 63

2,2-DIPHENYL-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PROPYL)PROPANAMIDE:

Example 63 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 2,2-diphenyl)propanoic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.14 (m, 14H), 6.78 (d, 1H, J = 6.0 Hz), 6.73 (d, 1H, J = 6.0 Hz), 6.25 (s, 1H), 3.39 (dd, 2H, J = 6.4, 12.0 Hz), 2.90-2.80 (m, 2H), 2.40 (t, 2H, J =

6.8 Hz), 2.22 (t, 2H, J = 12.0 Hz), 2.05-1.90 (m, 2H), 2.02 (s, 3H), 1.77-1.65 (m, 2H), 1.35-1.20 (m, 2H); ESMS m/e: 451.4 $(M + H)^+$.

Example 64

2,2,2-TRIPHENYL-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL) PROPYL) ACETAMIDE:

Example 64 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 2,2,2-triphenylacetic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.15 (m, 19H), 6.78 (d, 1H, J = 5.6 Hz), 6.72 (d, 1H, J = 6.0 Hz), 6.29 (s, 1H), 3.45 (dd, 2H, J = 6.6, 12.0 Hz), 2.89-2.89 (m, 2H), 2.39 (t, 2H, J = 6.8 Hz), 2.21 (t, 2H, J = 11.8 Hz), 2.04-1.92 (m, 2H), 1.80-1.65 (m, 2H), 1.35-1.20 (m, 2H); ESMS m/e: 513.3 $(M + H)^+$.

Example 65

2-(4-CHLOROPHENYL)-2-METHYL-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL) PROPYL) PROPANAMIDE:

Example 65 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 2-(4-chlorophenyl)-2-methyl)propanoic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.18 (m, 8H), 6.79 (d, 1H, J = 6.0 Hz), 6.74 (d, 1H, J = 5.6 Hz), 6.50 (s, 1H), 3.34 (dd, 2H, J = 6.2, 11.8 Hz), 2.93-2.84 (m, 2H), 2.45 (t, 2H, J = 6.6 Hz), 2.30-2.18 (m, 2H), 2.08-1.93 (m, 2H), 1.75-1.63 (m, 2H), 1.60 (s, 6H), 1.30 (d, 2H, 11.6 Hz); ESMS m/e: 423.3 $(M + H)^+$.

Example 66

2-(4-CHLOROPHENYL)-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL) PROPYL) PROPANAMIDE:

Example 66 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 2-(4-chlorophenyl)propanoic acid according to the procedures

described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.18 (m, 9H), 6.81 (d, 1H, J = 6.0 Hz), 6.76 (d, 1H, J = 5.6 Hz), 3.53 (q, 1H, J = 7.2 Hz), 3.40-3.30 (m, 2H), 3.03-2.86 (m, 2H), 2.49 (dt, 2H, J = 2.0, 6.8 Hz), 2.29 (t, 2H, J = 12.0 Hz), 2.17-2.02 (m, 2H), 1.75-1.66 (m, 2H), 1.53 (d, 3H, J = 7.2 Hz), 1.43-1.30 (m, 2H); ESMS m/e: 409.3 (M + H)$^+$.

Example 67

2,2-BIS(4-FLUOROPHENYL)-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 67 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 2,2-bis(4-fluorophenyl)acetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.10 (m, 9H), 7.05-6.97 (m, 4H), 6.79 (d, 1H, J = 5.6 Hz), 6.75 (d, 1H, J = 5.6 Hz), 4.83 (s, 1H), 3.43 (dd, 2H, J = 6.0, 11.6 Hz), 2.98-2.90 (m, 2H), 2.53 (t, 2H, J = 6.6 Hz), 2.29 (t, 2H, J = 12.2 Hz), 2.10-1.96 (m, 2H), 1.80-1.70 (m, 2H), 1.34 (d, 2H, J = 13.2 Hz); ESMS m/e: 473.3 (M + H)$^+$.

Example 68

2,2-BIS(4-CHLOROPHENYL)-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 68 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 2,2-bis(4-chlorophenyl)acetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.15 (m, 13H), 6.79 (d, 1H, J = 5.6 Hz), 6.75 (d, 1H, J = 5.6 Hz), 4.80 (s, 1H), 3.42 (dd, 2H, J = 6.0, 11.6 Hz), 3.00-2.85 (m, 2H), 2.52 (t, 2H, J = 6.4 Hz), 2.29 (t, 2H, J = 11.0 Hz), 2.10-1.90 (m, 2H), 1.80-1.65 (m, 2H), 1.34 (d, 2H, J = 12.4 Hz); ESMS m/e: 505.2 (M + H)$^+$.

Example 69

[(4-CHLOROPHENYL)CYCLOPENTYL]-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 69 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 1-(4-chlorophenyl)cyclopentanecarboxylic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.16 (m, 8H), 6.81 (d, 1H, J = 5.6 Hz), 6.75 (d, 1H, J = 5.6 Hz), 6.46 (s, 1H), 3.30 (dd, 2H, J = 5.6, 12.0 Hz), 2.95-2.87 (m, 2H), 2.59-2.49 (m, 2H), 2.41 (t, 2H, J = 6.4 Hz), 2.25 (t, 2H, J = 11.0 Hz), 2.17-1.95 (m, 4H), 1.90-1.60 (m, 6H), 1.35 (d, 2H, J = 12.4 Hz); ESMS m/e: 449.3 $(M + H)^+$.

Example 70

[(4-FLUOROPHENYL)CYCLOPENTYL]-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 70 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 1-(4-fluorophenyl)cyclopentanecarboxylic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 4H), 7.30-7.15 (m, 2H), 7.01 (t, 2H, J = 8.4 Hz), 6.81 (d, 1H, J = 6.4 Hz), 6.75 (d, 1H, J = 6.0 Hz), 6.45 (s, 1H), 3.30 (dd, 2H, J = 6.0, 12.0 Hz), 2.96-2.86 (m, 2H), 2.59-2.50 (m, 2H), 2.41 (t, 2H, J = 6.4 Hz), 2.24 (t, 2H, J = 11.8 Hz), 2.17-2.05 (m, 2H), 2.04-1.92 (m, 2H), 1.89-1.60 (m, 6H), 1.33 (d, 2H, J = 12.8 Hz); ESMS m/e: 433.4 $(M + H)^+$.

Example 71

[(4-CHLOROPHENYL)CYCLOHEXYL]-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 71 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 1-(4-

chlorophenyl)cyclohexanecarboxylic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.18 (m, 9H), 6.81 (d, 1H, J = 5.2 Hz), 6.75 (d, 1H, J = 6.0 Hz), 3.32 (dd, 2H, J = 6.0, 11.6 Hz), 2.96-2.86 (m, 2H), 2.42 (t, 2H, J = 6.4 Hz), 2.40-2.32 (m, 2H), 2.29-2.18 (m, 2H), 2.16-2.05 (m, 2H), 1.98-1.85 (m, 2H), 1.71-1.56 (m, 8H), 1.34 (d, 2H, J = 12.8 Hz); ESMS m/e: 463.3 (M + H)$^+$.

Example 72

[(4-FLUOROPHENYL)CYCLOHEXYL]-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 72 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 1-(4-fluorophenyl)cyclohexanecarboxylic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.38 (m, 2H), 7.36-7.30 (m, 2H), 7.28-7.18 (m, 3H), 7.01 (t, 2H, J = 8.6 Hz), 6.80 (d, 1H, J = 6.0 Hz), 6.75 (d, 1H, J = 5.6 Hz), 3.32 (dd, 2H, J = 5.8, 12.2 Hz), 2.97-2.88 (m, 2H), 2.43 (t, 2H, J = 6.4 Hz), 2.40-2.32 (m, 2H), 2.3-2.20 (m, 2H), 2.18-2.08 (m, 2H), 1.99-1.84 (m, 2H), 1.69 (t, 2H, J = 6.4 Hz), 1.65-1.55 (m, 6H), 1.34 (d, 2H, J = 14.0 Hz); ESMS m/e: 447.3 (M + H)$^+$.

Example 73

[(4-CHLOROPHENYL)CYCLOPROPYL]-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 73 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 1-(4-chlorophenyl)cyclopropanecarboxylic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.13 (m, 8H), 6.81 (d, 1H, J = 5.2 Hz), 6.74 (d, 1H, J = 5.6 Hz), 5.59 (s, 1H), 3.28 (dd, 2H, J = 6.8, 12.8 Hz), 2.90-2.82 (m, 2H), 2.40 (t, 2H, J = 7.2 Hz), 2.26 (dt, 2H, J = 2.0, 11.8 Hz), 2.12-2.00 (m, 2H), 1.71-1.58

(m, 4H), 1.35-1.26 (m, 2H), 1.02 (dd, 2H, J = 3.8, 6.6 Hz); ESMS m/e: 421.3 $(M + H)^+$.

Example 74

[(4-CHLOROPHENYL)CYCLOBUTYL]-N-(3-(SPIRO[INDENE-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 74 was prepared from 3-(SPIRO[indene-1,4'-piperidine]-10-yl)propylamine and 1-(4-chlorophenyl)cyclobutanecarboxylic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.16 (m, 8H), 6.81 (d, 1H, J = 6.0 Hz), 6.75 (d, 1H, J = 5.2 Hz), 6.41 (s, 1H), 3.31 (dd, 2H, J = 5.8, 12.2 Hz), 2.97-2.80 (m, 4H), 2.53-2.45 (m, 2H), 2.42 (t, 2H, J = 6.6 Hz), 2.26 (t, 2H, J = 11.2 Hz), 2.20-1.85 (m, 4H), 1.75-1.65 (m, 2H), 1.35 (d, 2H, J = 12.0 Hz); ESMS m/e: 435.3 $(M + H)^+$.

Example 75

[(4-METHYL)PHENYL)CYCLOPENTYL]-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 75 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 1-(4-methyl)phenyl)cyclopentanecarboxylic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.33 (d, 1H, J = 7.1 Hz), 7.30-7.26 (m, 3H), 7.23-7.19 (m, 1H), 7.15-7.06 (m, 3H), 6.33-6.27 (m, 1H), 5.05 (s, 2H), 3.44-3.38 (m, 2H), 3.29-3.21 (m, 2H), 2.42-2.35 (m, 2H), 2.33-2.29 (m, 2H), 2.07 (s, 3H), 1.82-1.64 (m, 14H); ESMS m/e: 433.3 $(M + H)^+$.

Example 76

2,2-DIPHENYL-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 76 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine

and 2,2-diphenylacetyl chloride according to the procedures described in Scheme F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.72 (m, 1H), 7.48-7.37 (m, 4H), 7.37-7.25 (m, 7H), 7.25-7.16 (m, 3H), 5.06 (s, 2H), 5.04 (s, 1H), 3.52-3.38 (m, 2H), 3.33-3.17 (m, 2H), 3.11-2.92 (m, 2H), 2.92-2.77 (m, 2H), 2.76-2.60 (m, 2H), 2.22-2.05 (m, 2H), 1.72 (d, 2H, J = 14.0 Hz); ESMS m/e: 441.3 $(M + H)^+$.

Example 77

2,2,2-TRIPHENYL-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 77 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 2,2,2-triphenylacetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.24 (m, 11H), 7.22-7.11 (m, 8H), 2.95 (s, 1H), 2.90-2.83 (m, 2H), 2.78-2.72 (m, 2H), 2.48 (t, 2H, J = 6.8 Hz), 2.39-2.31 (m, 2H), 1.94 (dt, 2H, J = 4.2, 13.1), 1.77-1.63 (m, 5H); ESMS m/e: 517.0 $(M + H)^+$.

Example 78

2,2-BIS(4-METHYL)PHENYL)-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 78 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 2,2-bis(4-methyl)phenyl)acetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.23-7.19 (m, 1H), 7.19-7.15 (m, 4H), 7.14-7.04 (m, 5H), 6.77-6.69 (s, 1H), 5.13-5.00 (m, 2H), 4.87-4.79 (s, 1H), 3.49-3.30 (m, 2H), 2.82-2.67 (m, 2H), 2.50-2.38 (m, 2H), 2.38-2.27 (m, 2H), 2.33-2.27 (s, 6H), 1.92-1.76 (m, 2H), 1.76-1.63 (m, 4H); ESMS m/e: 469.3 $(M + H)^+$.

Example 79

[(4-FLUOROPHENYL)CYCLOPENTYL]-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 79 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 1-(4-fluorophenyl)cyclopentanecarboxylic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.10 (m, 9H), 5.00 (s, 2H), 3.32-3.10 (m, 4H), 3.00-2.85 (m, 2H), 2.70-2.50 (m, 4H), 2.40-2.30 (m, 2H), 2.00-1.84 (m, 4H), 1.84-1.55 (m, 6H); ESMS m/e: 437.3 $(M + H)^+$.

Example 80

[(4-FLUOROPHENYL)CYCLOHEXYL]-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 80 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 1-(4-fluorophenyl)cyclohexanecarboxylic acid according to the procedures described in Scheme E: ESMS m/e: 451.3 $(M + H)^+$.

Example 81

2-(4-CHLOROPHENYL)-2-METHYL-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)PROPANAMIDE:

Example 81 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 2-(4-chlorophenyl)-2-methyl)propanoic acid according to the procedures described in Scheme E: ESMS m/e: 427.2 $(M + H)^+$.

Example 82

2-(4-FLUOROPHENYL)-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)PROPANAMIDE:

Example 82 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 2-(4-fluorophenyl)propanoic acid according to the procedures described in Scheme E: ESMS m/e: 397.3 $(M + H)^+$.

Example 83

2-(4-CHLOROPHENYL)-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)PROPANAMIDE:

Example 83 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 2-(4-chlorophenyl)propanoic acid according to the procedures described in Scheme E: ESMS m/e: 413.3 $(M + H)^+$.

Example 84

2,2-BIS(4-FLUOROPHENYL)-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 84 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 2,2-bis(4-fluorophenyl)acetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.19 (m, 7H), 7.11-6.98 (m, 6H), 5.06 (s, 2H), 4.81 (s, 1H), 3.35 (dd, 2H, J = 6.0, 12.0 Hz), 2.82-2.70 (m, 2H), 2.47 (t, 2H, J = 6.4 Hz), 2.36 (dt, 2H, J = 2.8, 12.0 Hz), 1.88-1.68 (m, 6H); ESMS m/e: 477.3 $(M + H)^+$.

Example 85

[(4-CHLOROPHENYL)CYCLOPENTYL]-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 85 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine

and 1-(4-chlorophenyl)cyclopentanecarboxylic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-6.92 (m, 9H), 5.00 (s, 2H), 3.35-3.10 (m, 4H), 3.00-2.85 (m, 2H), 2.61-2.49 (m, 4H), 2.40-2.35 (m, 2H), 2.00-1.80 (m, 4H), 1.80-1.57 (m, 6H); ESMS m/e: 453.2 $(M + H)^+$.

Example 86

2-(3,4-DIFLUOROPHENYL)-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 86 was prepared from 3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propylamine and 2-(3,4-difluorophenyl)acetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.24-7.07 (m, 5H), 7.05-7.00 (m, 1H), 5.06 (s, 2H), 3.49 (s, 2H), 3.39-3.32 (m, 2H), 2.96-2.87 (m, 2H), 2.59-2.49 (m, 4H), 2.05-1.94 (m, 2H), 1.85-1.73 (m, 4H); ESMS m/e: 401.2 $(M + H)^+$.

Example 87

[(4-CHLOROPHENYL)CYCLOBUTYL]-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 87 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 1-(4-chlorophenyl)cyclobutanecarboxylic acid according to the procedures described in Scheme E: ESMS m/e: 439.3 $(M + H)^+$.

Example 88

2,2-DIPHENYL-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)PROPANAMIDE:

Example 88 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine

and 2,2-diphenyl)propanoic acid according to the procedures described in Scheme E: ESMS m/e: 455.4 $(M + H)^+$.

Example 89

[(4-CHLOROPHENYL)CYCLOPROPYL]-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)CARBOXAMIDE:

Example 89 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 1-(4-chlorophenyl)cyclopropanecarboxylic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.10 (m, 9H), 5.01 (s, 2H), 3.55-3.33 (m, 2H), 3.27-3.17 (m, 2H), 3.14-2.98 (m, 2H), 2.94-2.83 (m, 2H), 2.74-2.57 (m, 2H), 2.08-1.95 (m, 1H), 1.87-1.75 (m, 2H), 1.60-1.45 (m, 3H), 1.21-0.91 (m, 2H); ESMS m/e: 425.2 $(M + H)^+$.

Example 90

2,2-BIS(4-CHLOROPHENYL)-N-(3-(SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL)ACETAMIDE:

Example 90 was prepared from (3-(SPIRO[1,3-dihydroisobenzofuran-1,4'-piperidine]-10-yl)propyl)amine and 2,2-bis(4-chlorophenyl)acetic acid according to the procedures described in Scheme E: ESMS m/e: 509.2 $(M + H)^+$.

Example 91

2,2-BIS(4-CHLOROPHENYL)-N-[3-(1-OXOSPIRO[INDANE-2,4'-PIPERIDINE]-10-YL)PROPYL]ACETAMIDE:

Example 91 was prepared from 10-(3-aminopropyl)spiro[indane-2,4'-piperidine]-1-one and 2,2-bis(4-chlorophenyl)acetic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.70 (d, 1H, J = 7.6 Hz), 7.54 (dt, 1H, J = 1.2, 7.6 Hz), 7.41-7.04 (m, 10H), 4.71 (s, 1H), 3.32 (dd, 2H, J = 5.6, 11.6 Hz), 2.92 (s, 2H), 2.90-2.82 (m, 2H), 2.51-2.39

(m, 1H), 2.22-1.99 (m, 2H), 1.90-1.77 (m, 2H), 1.69-1.55 (m, 2H), 1.41-1.27 (m, 2H), 1.18(t, 1H, J = 7.0 Hz); ESMS m/e: 521.1 $(M + H)^+$.

Example 92

2,2-BIS(4-FLUOROPHENYL)-N-[3-(1-OXOSPIRO[INDANE-2,4'-PIPERIDINE]-10-YL)PROPYL]ACETAMIDE:

Example 92 was prepared from 10-(3-aminopropyl)spiro[indane-2,4'-piperidine]-1-one and 2,2-bis(4-fluorophenyl)acetic acid according to the procedures described in Scheme E: ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.71 (d, 1H, J = 7.6 Hz), 7.54 (d, 1H, J = 7.6 Hz), 7.36-7.25 (m, 6H), 6.97-6.87 (m, 4H), 4.75 (s, 1H), 3.34 (dd, 2H, J = 5.6, 11.6 Hz), 2.94 (s, 2H), 2.90-2.73 (m, 2H), 2.40 (t, 1H, J = 5.8 Hz), 2.20-1.92 (m, 2H), 1.85 (dt, 2H, J = 3.6, 13.2 Hz), 1.68-1.55 (m, 2H), 1.30 (d, 2H, J = 12.4 Hz), 1.18(t, 1H, J = 7.2 Hz); ESMS m/e: 489.2 $(M + H)^+$.

Example 93

N-[3-(1-OXOSPIRO[3-HYDROISOBENZOFURAN-3,4'-PIPERIDINE]-10-YL)PROPYL]-2,2-DIPHENYLACETAMIDE:

Example 93 as prepared from 10-(3-aminopropyl)spiro[3-hydroisobenzofuran-3,4'-piperidine]-1-one and 2,2-diphenylacetyl chloride according to the procedures described in Scheme F: ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, 1H, J = 7.6 Hz), 7.83-7.69 (m, 1H), 7.69-7.55 (m, 3H), 7.49-7.37 (m, 4H), 7.37-7.26 (m, 4H), 7.26-7.16 (m, 2H), 5.20 (s, 1H), 3.57-3.42 (m, 2H), 3.41-3.25 (m, 2H), 3.17-2.98 (m, 4H), 2.98-2.81 (m, 2H), 2.26-2.02 (m, 2H), 1.80-1.61 (m, 2H); ESMS m/e: 455.3 $(M + H)^+$.

Example 94

2,2-BIS(4-CHLOROPHENYL)-N-[3-(1-OXOSPIRO[3-HYDROISOBENZOFURAN-3,4'-PIPERIDINE]-10-YL)PROPYL]ACETAMIDE:

Example 94 was prepared from 10-(3-aminopropyl)spiro[3-hydroisobenzofuran-3,4'-piperidine]-1-one and 2,2-bis(4-chlorophenyl)acetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 2H, J = 8.2 Hz), 7.66 (apparent t, 2H, J = 7.6 Hz), 7.53 (t, 2H, J = 6.9 Hz), 7.44 (d, 2H, J = 6.9 Hz), 7.26-7.14 (m, 5H), 4.86 (s, 1H), 3.40-3.29 (m, 4H), 3.08-2.98 (m, 3H), 2.57 (m, 2H), 2.1 (m, 2H), 1.73-1.65 (m, 3H); ESMS m/e: 523.1 $(M + H)^+$.

Example 95

2,2-BIS(4-FLUOROPHENYL)-N-[3-(1-OXOSPIRO[3-HYDROISOBENZOFURAN-3,4'-PIPERIDINE]-10-YL)PROPYL]ACETAMIDE:

Example 95 was prepared from 10-(3-aminopropyl)spiro[3-hydroisobenzofuran-3,4'-piperidine]-1-one and 2,2-bis(4-fluorophenyl)acetic acid according to the procedures described in Scheme E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, 1H, J = 7.0 Hz), 7.61 (apparent t, 1H, J = 6.9 Hz), 7.46 (apparent t, 1H, J = 7.4 Hz), 7.29 (d, 1H, J = 7.4 Hz), 7.21-7.14 (m, 4H), 7.10-7.01 (m, 1H), 6.98-6.90 (m, 3H), 6.48 (m, 1H), 4.48 (s, 1H), 3.37-3.29 (m, 2H), 2.80-2.73 (m, 2H), 2.46-2.37 (m, 4H), 2.08-1.97 (m, 3H), 1.71-1.58 (m, 3H); ESMS m/e: 491.3 $(M + H)^+$.

Example 96

2,2-DIPHENYL-N-(3-(SPIRO[1,2,3,4-TETRAHYDRONAPHTHALENE-1,4'-PIPERIDINE]-11-YL)PROPYL)ACETAMIDE:

Example 96 was prepared from 3-(SPIRO[1,2,3,4-tetrahydronaphthalene-1,4'-piperidine]-11-yl)propylamine and 2,2-diphenylacetic acid according to the procedures described in Scheme F: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.00 (m, 15H), 4.87 (s, 1H), 3.36 (dd, 2H, J = 5.6, 12.0 Hz), 2.91 (d, 2H, J = 7.2 Hz), 2.75 (t, 2H, J = 6.0 Hz), 2.59 (t, 2H, J = 6.8 Hz), 2.37 (t, 2H, J = 12.0 Hz), 2.18 (dt,

2H, J = 3.6, 13.8 Hz), 1.86-1.66 (m, 6H), 1.59 (d, 2H, J = 14.0 Hz); ESMS m/e: 453.4 $(M + H)^+$.

Example 97

2,2-BIS(4-METHYL)PHENYL)-N-[3-(2-OXOSPIRO[1,3,4-TRIHYDRONAPHTHALENE-1,4'-PIPERIDINE]-11-YL)PROPYL]ACETAMIDE:

Example 97 was prepared from 11-(3-aminopropyl)spiro[1,3,4-trihydronaphthalene-1,4'-piperidine]-2-one and 2,2-bis(4-methyl)phenyl)acetic acid according to the procedures described in Scheme E: ESMS m/e: 495.3 $(M + H)^+$.

Example 98

N-[3-(2-OXOSPIRO[1,3,4-TRIHYDRONAPHTHALENE-1,4'-PIPERIDINE]-11-YL)PROPYL]-2,2-DIPHENYLACETAMIDE:

Example 98 was prepared from 11-(3-aminopropyl)spiro[1,3,4-trihydronaphthalene-1,4'-piperidine]-2-one and 2,2-diphenylacetic acid according to the procedures described in Scheme E: ESMS m/e: 467.2 $(M + H)^+$.

Example 99

2,2-DIPHENYL-N-[3-(4,5,6-TRIFLUOROSPIRO[1,3-DIHYDROISOBENZOFURAN-3,4'-PIPERIDINE]-10-YL)PROPYL]ACETAMIDE:

Example 99 was prepared from 4,5,6-trifluorospiro[1,3-dihydroisobenzofuran-3,4'-piperidine] and N-(3-bromopropyl)-2,2-diphenylacetamide according to the procedures described in Scheme H: ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 8H), 7.27-7.21 (m, 2H), 7.15 (br, 1H), 6.84-6.77 (m, 1H), 5.01 (s, 2H), 4.86 (s, 1H), 3.40 (dd, 2H, J = 6.0, 12.0 Hz), 2.84-2.76 (m, 2H), 2.47 (t, 2H, J = 6.4 Hz), 2.34 (t, 2H, J = 11.4 Hz), 2.21-2.10 (m, 2H), 1.78-1.68 (m, 2H); ESMS m/e: 495.4 $(M + H)^+$.

Example 100

N-[3-(5-CHLOROSPIRO[1,3-DIHYDROISOBENZOFURAN-3,4'-PIPERIDINE]-10-YL)PROPYL]-2, 2-DIPHENYLACETAMIDE:

Example 100 was prepared from 5-chlorospiro[1,3-dihydroisobenzofuran-3,4'-piperidine] and N-(3-bromopropyl)-2,2-diphenylacetamide according to the procedures described in Scheme H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.19 (m, 11H), 7.12 (d, 1H, J = 6.0 Hz), 7.05 (s, 1H), 6.77 (br, 1H), 4.99 (s, 2H), 4.91 (s, 1H), 3.40 (dd, 2H, J = 6.2, 11.8 Hz), 2.74 (d, 2H, J = 11.6 Hz), 2.42 (t, 2H, J = 6.8 Hz), 2.31 (dt, 2H, J = 3.8, 11.2 Hz), 1.78-1.68 (m, 6H); ESMS m/e: 475.4 (M + H)$^+$.

Example 101

N-[3-(5-FLUOROSPIRO[1,3-DIHYDROISOBENZOFURAN-3,4'-PIPERIDINE]-10-YL)PROPYL]-2, 2-DIPHENYLACETAMIDE:

Example 101 was prepared from 5-fluorospiro[1,3-dihydroisobenzofuran-3,4'-piperidine] and N-(3-bromopropyl)-2,2-diphenylacetamide according to the procedures described in Scheme H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.21 (m, 10H), 7.12-7.10 (m, 1H), 6.96 (dd, 1H, J = 2.4, 8.6 Hz), 6.81-6.72 (m, 2H), 5.00 (s, 2H), 4.91 (s, 1H), 3.40 (dd, 2H, J = 6.4, 12.6 Hz), 2.82-2.73 (m, 2H), 2.45 (t, 2H, J = 6.6 Hz), 2.35 (dt, 2H, J = 2.6, 12.4 Hz), 1.86-1.67 (m, 6H); ESMS m/e: 459.4 (M + H)$^+$.

Example 102

N-{3-[5-(METHYLETHYL)SPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL]PRO PYL}-2,2-DIPHENYLACETAMIDE:

Example 102 was prepared from 5-(methylethyl)spiro[1,3-dihydroisobenzofuran-1,4'-piperidine] and N-(3-bromopropyl)-2,2-diphenylacetamide according to the procedures described in Scheme H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 8H), 7.28-7.21 (m, 2H), 7.17-7.10 (m, 2H),

6.99 (br, 1H), 6.96 (s, 1H), 5.02 (s, 2H), 4.90 (s, 1H), 3.41 (dd, 2H, J = 5.6, 11.7 Hz), 2.83-2.74 (m, 2H), 2.46 (t, 2H, J = 6.6 Hz), 2.41-2.32 (m, 2H), 1.86 (dt, 2H, J = 4.4, 13.2 Hz), 1.78-1.69 (m, 4H), 1.23 (d, 6H, J = 6.7 Hz); ESMS m/e: 483.5 $(M + H)^+$.

Example 103

N-[3-(5-METHYLSPIRO[1,3-DIHYDROISOBENZOFURAN-1,4'-PIPERIDINE]-10-YL)PROPYL]-2, 2-DIPHENYLACETAMIDE:

Example 103 was prepared from 5-methylspiro[1,3-dihydroisobenzofuran-1,4'-piperidine] and N-(3-bromopropyl)-2,2-diphenylacetamide according to the procedures described in Scheme H: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 10H), 7.09 (d, 1H, J = 7.6 Hz), 7.04-6.96 (m, 2H), 6.85 (br, 1H), 5.01 (s, 2H), 4.89 (s, 1H), 3.39 (dd, 2H, J = 6.0, 12.0 Hz), 2.80-2.72 (m, 2H), 2.43 (t, 2H, J = 6.8 Hz), 2.37 (s, 3H), 2.38-2.28 (m, 2H), 1.87-1.76 (m, 4H), 1.75-1.66 (m, 2H); ESMS m/e: 455.5 $(M + H)^+$.

II. Synthetic Methods for General Structures

The examples described in Section I are merely illustrative of the methods used to synthesize MCH1 antagonists. Further derivatives may be obtained utilizing generalized methods based on the synthetic methods used to synthesize the examples.

It may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, carboxylic acid, and hydroxyl groups in the generalized synthetic methods to form further derivatives. Methods for protection and deprotection of such groups are well-known in the art, and may be found, for example in Green, T.W. and Wuts, P.G.M. (1991) Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

III. Oral Compositions

As a specific embodiment of an oral composition of a compound of this invention, 100 mg of one of the compounds described herein is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

IV. Pharmacological Evaluation of Compounds at Cloned rat MCH1 Receptor

The pharmacological properties of the compounds of the present invention were evaluated at the cloned rat MCH1 receptor using protocols described below.

Host Cells

A broad variety of host cells can be used to study heterologously expressed proteins. These cells include but are not restricted to assorted mammalian lines. such as: Cos-7, CHO, LM(tk-), HEK293, Peak rapid 293, etc.;

insect cell lines such as: Sf9, Sf21, etc.; amphibian cells such as xenopus oocytes; and others.

COS 7 cells are grown on 150 mm plates in DMEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 Fg/ml streptomycin) at 37°C, 5% CO_2. Stock plates of COS-7 cells are trypsinized and split 1:6 every 3-4 days.

Human embryonic kidney 293 cells are grown on 150 mm plates in DMEM with supplements (10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 Fg/ml streptomycin) at 37°C, 5% CO_2. Stock plates of 293 cells are trypsinized and split 1:6 every 3-4 days.

Human embryonic kidney Peak rapid 293 (Peakr293) cells are grown on 150 mm plates in DMEM with supplements (10% fetal bovine serum, 10% L-glutamine, 50 Fg/ml gentamycin) at 37°C, 5% CO_2. Stock plates of Peak rapid 293 cells are trypsinized and split 1:12 every 3-4 days.

Mouse fibroblast LM(tk-) cells are grown on 150 mm plates in DMEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 Fg/ml streptomycin) at 37°C, 5% CO_2. Stock plates of LM(tk-) cells are trypsinized and split 1:10 every 3-4 days.

Chinese hamster ovary (CHO) cells were grown on 150 mm plates in HAM=s F-12 medium with supplements (10% bovine calf serum, 4 mM L-glutamine and 100 units/ml penicillin/ 100 Fg/ml streptomycin) at 37°C, 5% CO_2. Stock plates of CHO cells are trypsinized and split 1:8 every 3-4 days.

Mouse embryonic fibroblast NIH-3T3 cells are grown on 150 mm plates in Dulbecco=s Modified Eagle Medium (DMEM) with

supplements (10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 Fg/ml streptomycin) at 37°C, 5% CO_2. Stock plates of NIH-3T3 cells are trypsinized and split 1:15 every 3-4 days.

Sf9 and Sf21 cells are grown in monolayers on 150 mm tissue culture dishes in TMN-FH media supplemented with 10% fetal calf serum, at 27°C, no CO_2. High Five insect cells are grown on 150 mm tissue culture dishes in Ex-Cell 400™ medium supplemented with L-Glutamine, also at 27°C, no CO_2.

In some cases, cell lines that grow as adherent monolayers can be converted to suspension culture to increase cell yield and provide large batches of uniform assay material for routine receptor screening projects.

Transient expression

DNA encoding proteins to be studied can be transiently expressed in a variety of mammalian, insect, amphibian and other cell lines by several methods including but not restricted to; calcium phosphate-mediated, DEAE-dextran mediated, Liposomal-mediated, viral-mediated, electroporation-mediated and microinjection delivery. Each of these methods may require optimization of assorted experimental parameters depending on the DNA, cell line, and the type of assay to be subsequently employed.

A typical protocol for the calcium phosphate method as applied to Peak rapid 293 cells is described as follows:

Adherent cells are harvested approximately twenty-four hours before transfection and replated at a density of 3.5 x 10^6 cells/dish in a 150 mm tissue culture dish and allowed to incubate over night at 37°C at 5% CO_2. 250 Fl of a mixture of $CaCl_2$ and DNA (15 Fg DNA in 250 mM $CaCl_2$) is added to a 5 ml plastic tube and 500 Fl of 2X HBS (280 mM

NaCl, 10 mM KCl, 1.5 mM Na_2HPO_4, 12 mM dextrose, 50 mM HEPES) is slowly added with gentle mixing. The mixture is allowed to incubate for 20 minutes at room temperature to allow a DNA precipitate to form. The DNA precipitate mixture is then added to the culture medium in each plate and incubated for 5 hours at 37°C, 5% CO_2. After the incubation, 5ml of culture medium (DMEM, 10% FBS, 10% L-glut and 50 g/ml gentamycin) is added to each plate. The cells are then incubated for 24 to 48 hours at 37°C, 5% CO_2.

A typical protocol for the DEAE-dextran method as applied to Cos-7 cells is described as follows; Cells to be used for transfection are split 24 hours prior to the transfection to provide flasks which are 70-80% confluent at the time of transfection. Briefly, 8 Fg of receptor DNA plus 8 Fg of any additional DNA needed (e.g. G protein expression vector, reporter construct, antibiotic resistance marker, mock vector, etc.) are added to 9 ml of complete DMEM plus DEAE-dextran mixture (10 mg/ml in PBS). Cos-7 cells plated into a T225 flask (sub-confluent) are washed once with PBS and the DNA mixture is added to each flask. The cells are allowed to incubate for 30 minutes at 37°C, 5% CO_2. Following the incubation, 36 ml of complete DMEM with 80 FM chloroquine is added to each flask and allowed to incubate an additional 3 hours. The medium is then aspirated and 24 ml of complete medium containing 10% DMSO for exactly 2 minutes and then aspirated. The cells are then washed 2 times with PBS and 30 ml of complete DMEM added to each flask. The cells are then allowed to incubate over night. The next day the cells are harvested by trypsinization and reseeded as needed depending upon the type of assay to be performed.

A typical protocol for liposomal-mediated transfection as applied to CHO cells is described as follows; Cells to be used for transfection are split 24 hours prior to the

transfection to provide flasks which are 70-80% confluent at the time of transfection. A total of 10Fg of DNA which may include varying ratios of receptor DNA plus any additional DNA needed (e.g. G protein expression vector, reporter construct, antibiotic resistance marker, mock vector, etc.) is used to transfect each 75 cm^2 flask of cells. Liposomal mediated transfection is carried out according to the manufacturer=s recommendations (LipofectAMINE, GibcoBRL, Bethesda, MD). Transfected cells are harvested 24 hours post transfection and used or reseeded according the requirements of the assay to be employed.

A typical protocol for the electroporation method as applied to Cos-7 cells is described as follows; Cells to be used for transfection are split 24 hours prior to the transfection to provide flasks which are subconfluent at the time of transfection. The cells are harvested by trypsinization resuspended in their growth media and counted. 4 x 10^6 cells are suspended in 300 Fl of DMEM and placed into an electroporation cuvette. 8 Fg of receptor DNA plus 8 Fg of any additional DNA needed (e.g. G protein expression vector, reporter construct, antibiotic resistance marker, mock vector, etc.) is added to the cell suspension, the cuvette is placed into a BioRad Gene Pulser and subjected to an electrical pulse (Gene Pulser settings: 0.25 kV voltage, 950 FF capacitance). Following the pulse, 800 Fl of complete DMEM is added to each cuvette and the suspension transferred to a sterile tube. Complete medium is added to each tube to bring the final cell concentration to 1 x 10^5 cells/100 Fl. The cells are then plated as needed depending upon the type of assay to be performed.

A typical protocol for viral mediated expression of heterologous proteins is described as follows for baculovirus infection of insect Sf9 cells. The coding

region of DNA encoding the receptor disclosed herein may be subcloned into pBlueBacIII into existing restriction sites or sites engineered into sequences 5' and 3' to the coding region of the polypeptides. To generate baculovirus, 0.5 Fg of viral DNA (BaculoGold) and 3 Fg of DNA construct encoding a polypeptide may be co-transfected into 2 x 10^6 *Spodoptera frugiperda* insect Sf9 cells by the calcium phosphate co-precipitation method, as outlined in by Pharmingen (in "Baculovirus Expression Vector System: Procedures and Methods Manual"). The cells then are incubated for 5 days at 27°C. The supernatant of the co-transfection plate may be collected by centrifugation and the recombinant virus plaque purified. The procedure to infect cells with virus, to prepare stocks of virus and to titer the virus stocks are as described in Pharmingen=s manual. Similar principals would in general apply to mammalian cell expression via retro-viruses, Simliki forest virus and double stranded DNA viruses such as adeno-, herpes-, and vacinia-viruses, and the like.

Stable expression

Heterologous DNA can be stably incorporated into host cells, causing the cell to perpetually express a foreign protein. Methods for the delivery of the DNA into the cell are similar to those described above for transient expression but require the co-transfection of an ancillary gene to confer drug resistance on the targeted host cell. The ensuing drug resistance can be exploited to select and maintain cells that have taken up the

heterologous DNA. An assortment of resistance genes are available including but not restricted to Neomycin, Kanamycin, and Hygromycin. For the purposes of receptor studies, stable expression of a heterologous receptor protein is carried out in, but not necessarily restricted to, mammalian cells including, CHO, HEK293, LM(tk-), etc.

Cell membrane preparation

For binding assays, pellets of transfected cells are suspended in ice-cold buffer (20 mM Tris.HCl, 5 mM EDTA, pH 7.4) and homogenized by sonication for 7 sec. The cell lysates are centrifuged at 200 x g for 5 min at 4°C. The supernatants are then centrifuged at 40,000 x g for 20 min at 4°C. The resulting pellets are washed once in the homogenization buffer and suspended in binding buffer (see methods for radioligand binding). Protein concentrations are determined by the method of Bradford (1976) using bovine serum albumin as the standard. Binding assays are usually performed immediately, however it is possible to prepare membranes in batch and store frozen in liquid nitrogen for future use.

Radioligand binding assays

Radioligand binding assays for the rat MCH1 receptor were carried out using plasmid pcDNA3.1-rMCH1-f (ATCC Patent Deposit Designation No. PTA-3505). Plasmid pcDNA3.1-rMCH1-f comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to DNA encoding the rat MCH1 receptor so as to permit expression thereof. Plasmid pcDNA3.1-rMCH1-f was deposited on July 05, 2001, with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Patent Deposit Designation No. PTA-3505.

Binding assays can also be performed as described hereinafter using plasmid pEXJ.HR-TL231 (ATCC Accession No. 203197) Plasmid pEXJ.HR-TL231 encodes the human MCH1 receptor and was deposited on September 17, 1998, with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Accession No. 203197.

Human embryonic kidney Peak rapid 293 cells (Peakr293 cells) were transiently transfected with DNA encoding the MCH1 receptor utilizing the calcium phosphate method and cell membranes were prepared as described above. Binding experiments with membranes from Peakr293 cells transfected with the rat MCH1 receptor were performed with 0.08 nM [^{3}H]Compound A (custom labeled by Amersham) (the synthesis of Compound A is described in detail below) using an incubation buffer consisting of 50 mM Tris pH 7.4, 10 mM $MgCl_2$, 0.16 mM PMSF, 1 mM 1,10 phenantroline and 0.2% BSA. Binding was performed at 25°C for 90 minutes. Incubations were terminated by rapid vacuum filtration over GF/C glass fiber filters, presoaked in 5% PEI using 50 nM Tris pH 7.4 as wash buffer. In all experiments, nonspecific binding is defined using 10 FM Compound A.

Functional assays

Cells may be screened for the presence of endogenous mammalian receptor using functional assays. Cells with no or a low level of endogenous receptor present may be transfected with the exogenous receptor for use in functional assays.

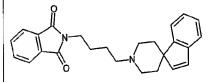
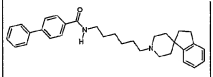
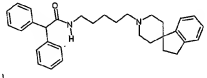
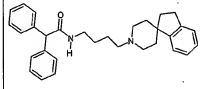
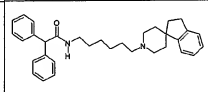
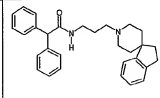
A wide spectrum of assays can be employed to screen for receptor activation. These range from traditional

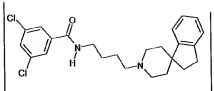
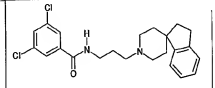
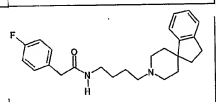
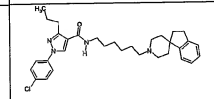
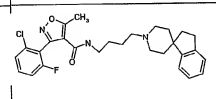
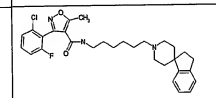
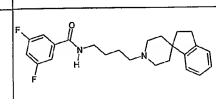
measurements of phosphatidyl inositol, cAMP, Ca^{++}, and K^{+}, for example; to systems measuring these same second messengers but which have been modified or adapted to be higher throughput, more generic, and more sensitive; to cell based platforms reporting more general cellular events resulting from receptor activation such as metabolic changes, differentiation, and cell division/proliferation, for example; to high level organism assays which monitor complex physiological or behavioral changes thought to be involved with receptor activation including cardiovascular, analgesic, orexigenic, anxiolytic, and sedation effects, for example.

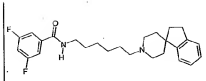
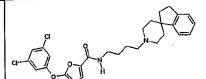
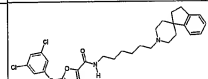
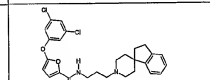
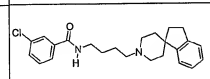
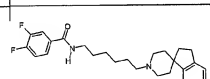
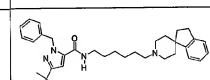
Radioligand Binding Assay Results

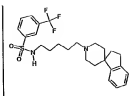
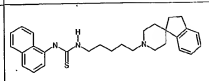
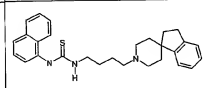
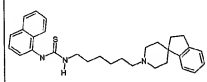
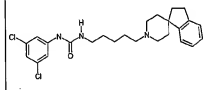
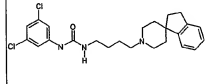
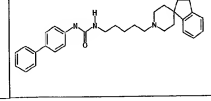
The compounds described above were assayed using cloned rat MCH1. The binding affinities of the compounds are shown in Table I.

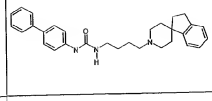
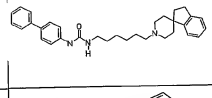
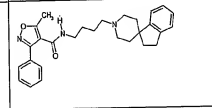
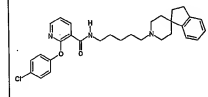
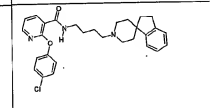
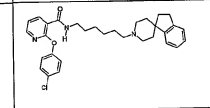
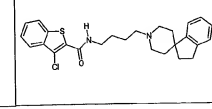
Table I

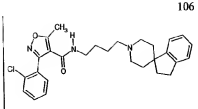
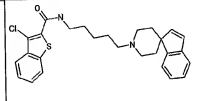
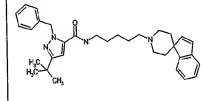
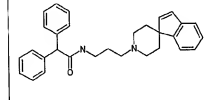
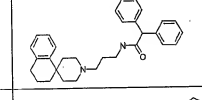
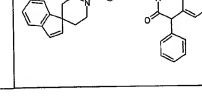
Example No.	STRUCTURE	KI (nm)
1		806.7
2		969.8
3		378.1
4		213.9
5		732.4
6		33.8

7		271.0
8		914.0
9		691.5
10		763.6
11		244.9
12		660.7
13		270.0

14		843.2
15		434.0
16		449.9
17		934.9
18		342.4
19		412.1
20		509.8

21		991.8
22		517.4
23		818.2
24		667.9
25		541.8.
26		511.6
27		662.2

28		549.1
29		430.7
30		655.6
31		212.5
32		387.8
33		430.8
34		882.8

35		824.7
36		736.4
37		793.7
38		6.5
39		128.4
40		384.4

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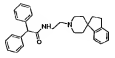
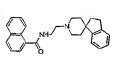
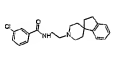
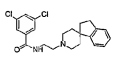
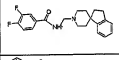
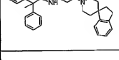
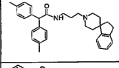
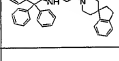
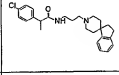
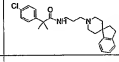
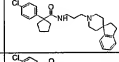
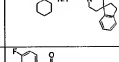
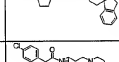
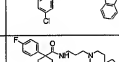
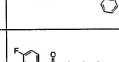
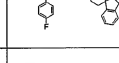
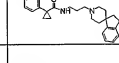
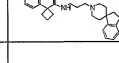
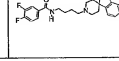
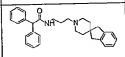
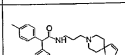
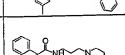
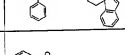
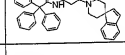
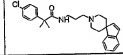
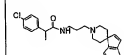
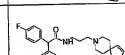
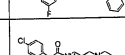
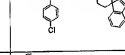
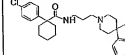
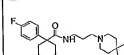
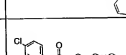
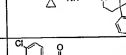
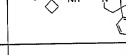
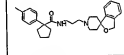
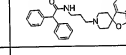
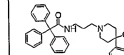
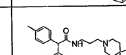
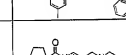
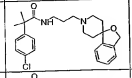
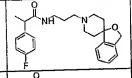
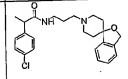
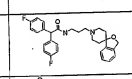
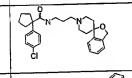
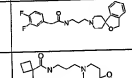
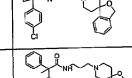
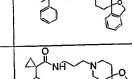
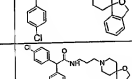
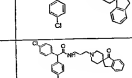
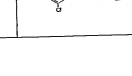
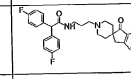
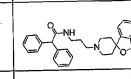
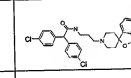
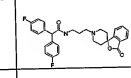
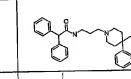
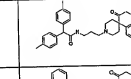
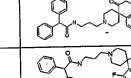
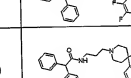
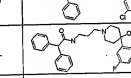
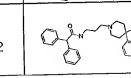
41		103
42		545
43		507
44		82.4
45		802
47		54.3
48		29.7
49		21.5
50		194

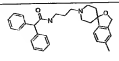
Example No.	Structure	Ki (nM)
46		84.1
52		112
53		56.9
54		208
55		8.6
56		108
57		4.2
58		150
59		175
60		42.3

Example No.	Structure	Ki (nM)
61		49
62		26
63		46
64		36
65		78
66		140
67		2.4
68		5.8
69		104
70		203

Example No.	Structure	Ki (nM)
71		71
72		131
73		239
74		185
75		700
76		20.6
77		151
78		19.7
79		514
80		174

Example No.	Structure	Ki (nM)
81		185
82		679
83		557
84		4.9
85		183
86		376
87		417
88		144
89		481
90		5.4
91		381

Example No.	Structure	Ki (nM)
92		61.6
93		783
94		600
95		84.6
96		128
97		428
98		682
99		11.6
100		2.6
101		5.8
102		162

103		14.7

V. Synthesis of Compound A

Described below is the synthesis of Compound A. Compound A is the radiolabeled compound that was used in the radioligand binding assays described above.

N-[3-(1,2,3,6-TETRAHYDRO-4-PYRIDINYL)PHENYL]ACETAMIDE: The reaction of saturated of aqueous Na_2CO_3 solution (25 mL), *tert*-butyl 4-{[(trifluoromethyl)sulfonyl]oxy}-1,2,3,6-tetrahydro-1-pyridine-carboxylate (20 mmol), 3-acetamidophenylboronic acid (30 mmol) and tetrakis-triphenyl)phosphine palladium (0) (1.15 g) in dimethoxyethane (40 mL) at reflux temperature overnight gave *tert*-butyl 4-[3-(acetylamino)phenyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate. Deprotection of the BOC group using HCl in dioxane followed by basification (pH 11-12) gave the desired product.

TERT-BUTYL *N*-(3-BROMOPROPYL)CARBAMATE: was prepared from 3-bromopropylamine hydrobromide and BOC_2O in the presence of base in dichloromethane.

N-{3-[1-(3-AMINOPROPYL)-1,2,3,6-TETRAHYDRO-4-PYRIDINYL]PHENYL}ACETAMIDE: The reaction of *tert*-butyl *N*-(3-bromopropyl)carbamate and *N*-[3-(1,2,3,6-tetrahydro-4-pyridinyl)phenyl]acetamide in refluxing dioxane with catalytic Bu_4NI and base as described in Scheme A gave *tert*-butyl 3-(4-[3-(acetylamino)phenyl]-3,6-dihydro-1(2*H*)-pyridinyl)propylcarbamate. Deprotection of the BOC group using HCl in dioxane followed by basification (pH 11-12) gave the desired product.

METHYL (4*S*)-3-({[3-(4-[3-(ACETYLAMINO)PHENYL]-3,6-DIHYDRO-1(2*H*)-PYRIDINYL)PROPYL]AMINO}CARBONYL)-4-(3,4-

DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: Prepared from the reaction of 5-methyl 1-(4-nitrophenyl) (6*S*)-6-(3,4-difluorophenyl)-4-(methoxymethyl)-2-oxo-3,6-dihydro-1,5(2*H*)-pyrimidinedicarboxylate (describe in PCT Publication No. WO 00/37026, published June 29, 2000) and *N*-{3-[1-(3-aminopropyl)-1,2,3,6-tetrahydro-4-pyridinyl]phenyl}acetamide: ^{1}H NMR 8.90 (t, 1 H, J=3.6 Hz), 7.75 (s, 1 H), 7.50-7.00 (m, 8 H), 6.68 (s, 1 H), 6.03 (br s, 1 H), 4.67 (s, 2 H), 3.71 (s, 3 H), 3.47 (s, 3 H), 3.38 (ABm, 2 H), 3.16 (m, 2 H), 2.71 (t, 2 H, J =5.4 Hz), 2.56 (m, 4 H), 2.35-1.90 (br, 2 H), 2.17 (s, 3 H), 1.82 (p, 2 H, J=7.2 Hz); ESMS, 612.25 $(M+H)^+$.

TRITIATED METHYL (4*S*)-3-{[(3-{4-[3-(ACETYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)AMINO]CARBONYL}-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: Methyl (4*S*)-3-({[3-(4-[3-(acetylamino)phenyl]-3,6-dihydro-1(2*H*)-pyridinyl)propyl]amino}carbonyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate was tritiated (Amersham) using the described cold method (H_2, balloon method, Methanol, Pd/C, overnight) to give the tritiated methyl (4*S*)-3-{[(3-{4-[3-(acetylamino)phenyl]-1-piperidinyl}propyl)amino]carbonyl}-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate ((+)-isomer), which in turn, was used as a radioligand in the MCH pharmacological assays.

VI. In-Vivo Methods

The following *in vivo* methods are performed to predict the efficacy of MCH1 antagonists for the treatment of obesity (3-day body weight and sweetened condensed milk), depression (forced swim test), anxiety (social interaction test), and urinary disorders (DIRC and CSTI).

Effects of MCH1 Antagonists on Body Weight (3 Day)

Male Long Evans rats (Charles River) weighing 180-200 grams are housed in groups of four on a 12 hour light/dark cycle with free access to food and water. Test compounds are administered twice daily *via* i.p. injection, 1 hour before the dark cycle and 2 hours after lights on, for three days. All rats are weighed daily after each morning injection. Overall results are expressed as body weight (grams) gained per day (mean ± SEM) and are analyzed by two-way ANOVA. Data for each time point are analyzed by one-way ANOVA followed by post hoc Newman-Keuls test. The data are analyzed using the GraphPad Prism (v2.01) (GraphPad Software, Inc., San Diego, CA). All data are presented as means ± S.E.M.

Effects of MCH1 Antagonists on Consumption of Sweetened Condensed Milk

Male C57BL/6 mice (Charles River) weighing 17-19 grams at the start of experiments are housed in groups of four or five on a 12 hour light/dark cycle with free access to food and water. For 7 days, mice are weighed, placed in individual cages and allowed to drink sweetened condensed milk (Nestle, diluted 1:3 with water) for 1 hour, 2-4 hours into the light cycle. The amount of milk consumed is determined by weighing the milk bottle before and after each drinking bout. On the test day, mice received i.p.

injections of Test Compound (3, 10 or 30 mg/kg in 0.01 % lactic acid), vehicle (0.01 % lactic acid) of d-fenfluramine (10 mg/kg in 0.01 % lactic acid) 30 min. prior to exposure to milk. The amount of milk consumed on the test day (in mls milk/ kg body weight) is compared to the baseline consumption for each mouse determined on the previous 2 days. Data for each time point are analyzed by one-way ANOVA.

Forced Swim Test (FST) in the Rat

Animals

Male Sprague-Dawley rats (Taconic Farms, NY) are used in all experiments. Rats are housed 5 per cage and maintained on a 12:12-h light-dark cycle. Rats are handled for 1 minutes each day for 4 days prior to behavioral testing.

Drug Administration

Animals are randomly assigned to receive a single i.p. administration of vehicle (2.5% EtOH / 2.5% Tween-80), imipramine (positive control; 60 mg/kg), or Test Compound 60 minutes before the start of the 5 minute test period. All injections are given using 1 cc tuberculin syringe with 26 3/8 gauge needles (Becton-Dickinson, VWR Scientific, Bridgeport, NJ). The volume of injection is 1 ml/kg.

Experimental Design

The procedure used in this study is similar to that previously described (Porsolt, et al., 1978), except the water depth is 31 cm in this procedure. The greater depth in this test prevents the rats from supporting themselves by touching the bottom of the cylinder with their feet. Swim sessions are conducted by placing rats in individual plexiglass cylinders (46 cm tall x 20 cm in diameter) containing 23-25°C water 31 cm deep. Swim tests are

conducted always between 900 and 1700 hours and consisted of an initial 15-min conditioning test followed 24h later by a 5-minute test. Drug treatments are administered 60 minutes, before the 5-minute test period. Following all swim sessions, rats are removed from the cylinders, dried with paper towels and placed in a heated cage for 15 minutes and returned to their home cages. All test sessions are videotaped using a color video camera and recorded for scoring later.

Behavioral Scoring

The rat's behavior is rated at 5 second intervals during the 5 minute test by a single individual, who is blind to the treatment condition. Scored behaviors are:

1. Immobility- rat remains floating in the water without struggling and is only making those movements necessary to keep its head above water;
2. Climbing - rat is making active movements with its forepaws in and out of the water, usually directed against the walls;
3. Swimming - rat is making active swimming motions, more than necessary to merely maintain its head above water, e.g. moving around in the cylinder; and
4. Diving - entire body of the rat is submerged.

Data Analysis

The forced swim test data (immobility, swimming, climbing, diving) are subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Newman-Keuls test. The data are analyzed using the GprahPad Prism(v2.01) (GraphPad Software, Inc., San Diego, CA). All data are presented as means ± S.E.M. All data are presented as means ± S.E.M.

Forced Swim Test (FST) in the Mouse

Animals

DBA/2 mice (Taconic Farms, NY) are used in all experiments. Animals are housed 5 per cage in a controlled environment under a 12:12 hour light:dark cycle. Animals are handled 1 min each day for 4 days prior to the experiment. This procedure included a mock gavage with a 1.5 inch feeding tube.

Drug Administration

Animals are randomly assigned to receive a single administration of vehicle (5% EtOH/5% Tween-80), Test Compound, or imipramine (60 mg/kg) by oral gavage 1 hour before the swim test.

Experimental Design

The procedure for the forced swim test in the mouse is similar to that described above for the rat, with some modifications. The cylinder used for the test is a 1 liter beaker (10.5cm diameter X 15 cm height) fill to 800ml (10cm depth) of 23-25°C water. Only one 5-minute swim test is conducted for each mouse, between 1300 and 1700 hours. Drug treatments are administered 30-60 minutes before the 5-minute test period. Following all swim sessions, mice are removed from the cylinders, dried with paper towels and placed in a heated cage for 15 minutes. All test sessions are videotaped using a Sony color video camera and recorder for scoring later.

Behavorial Scoring

The behavior during minutes 2-5 of the test is played back on a TV monitor and scored by the investigator. The total time spent immobile (animal floating with only minimal movements to remain afloat) and mobile (swimming and movements beyond those required to remain afloat) are recorded.

Data Analysis

The forced swim test data (time exhibiting immobility, mobility; seconds) are subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Newman-Keuls test. The data are analyzed using the GraphPad Prism (v2.01) (GraphPad Software, Inc., San Diego, CA). All data are presented as means ± S.E.M.

Social Interaction Test (SIT)

Rats are allowed to acclimate to the animal care facility for 5 days and are housed singly for 5 days prior to testing. Animals are handled for 5 minutes per day. The design and procedure for the Social Interaction Test is carried out as previously described by Kennett, et al. (1997). On the test day, weight matched pairs of rats (± 5%), unfamiliar to each other, are given identical treatments and returned to their home cages. Animals are randomly divided into 5 treatment groups, with 5 pairs per group, and are given one of the following i.p. treatments: Test Compound (10, 30 or 100 mg/kg), vehicle (1 ml/kg) or chlordiazepoxide (5 mg/kg). Dosing is 1 hour prior to testing. Rats are subsequently placed in a white perspex test box or arena (54 x 37 x 26 cm), whose floor is divided up into 24 equal squares, for 15 minutes. An air conditioner is used to generate background noise and to keep the room at approximately 74°F. All sessions are videotaped using a JVC camcorder (model GR-SZ1, Elmwood Park, NJ) with either TDK (HG ultimate brand) or Sony 30 minute videocassettes. All sessions are conducted between 1300 - 1630 hours. Active social interaction, defined as grooming, sniffing, biting, boxing, wrestling, following and crawling over or under, is scored using a stopwatch (Sportsline model no. 226, 1/100 sec. discriminability). The number of episodes of rearing (animal completely raises up its body on its hind limbs), grooming (licking, biting, scratching of body), and face ishing (i.e. hands are moved repeatedly over face), and number of squares

crossed are scored. Passive social interaction (animals are lying beside or on top of each other) is not scored. All behaviors are assessed later by an observer who is blind as to the treatment of each pair. At the end of each test, the box is thoroughly wiped with moistened paper towels.

Animals

Male albino Sprague-Dawley rats (Taconic Farms, NY) are housed in pairs under a 12 hr light dark cycle (lights on at 0700 hrs.) with free access to food and water.

Drug Administration

Test Compound is dissolved in 100% DMSO or 5% lactic acid, v/v (Sigma Chemical Co., St. Louis, MO). Chlordiazepoxide (Sigma Chemical Co., St. Louis, MO) is dissolved in double distilled water. The vehicle consists of 50% DMSO (v/v) or 100% dimethylacetamide (DMA). All drug solutions are made up 10 minutes prior to injection and the solutions are discarded at the end of the test day. The volume of drug solution administered is 1 ml/kg.

Data Analysis

The social interaction data (time interacting, rearing and squares crossed) are subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Student-Newman-Keuls test. The data are subjected to a test of normality (Shapiro-Wilk test). The data are analyzed using the GBSTAT program, version 6.5 (Dynamics Microsystems, Inc., Silver Spring, MD, 1997). All data are presented as means ∀ S.E.M.

In Vivo Models of the Micturition Reflex

The effects of compounds on the micturition reflex are assessed in the "distension-induced rhythmic contraction" (DIRC), as described in previous publications (e.g. Maggi et al, 1987; Morikawa et al, 1992), and Continuous Slow Transvesicular Infusion (CSTI) models in rats.

DIRC Model

Female Sprague Dawley rats weighing approximately 300 g are anesthetized with subcutaneous urethane (1.2 g/kg). The trachea is cannulated with PE240 tubing to provide a clear airway throughout the experiment. A midline abdominal incision is made and the left and right ureters are isolated. The ureters are ligated distally (to prevent escape of fluids from the bladder) and cannulated proximally with PE10 tubing. The incision is closed using 4-0 silk sutures, leaving the PE10 lines routed to the exterior for the elimination of urine. The bladder is canulated via the transurethral route using PE50 tubing inserted 2.5 cm beyond the urethral opening. This cannula is secured to the tail using tape and connected to a pressure transducer. To prevent leakage from the bladder, the cannula is tied tightly to the exterior urethral opening using 4-0 silk.

To initiate the micturition reflex, the bladder is first emptied by applying pressure to the lower abdomen, and then filled with normal saline in 100 increments (maximum = 2 ml) until spontaneous bladder contractions occurred (typically 20-40 mmHg at a rate of one contraction every 2 to 3 minutes. Once a regular rhythm is established, vehicle (saline) or Test Compounds are administered i.v. or i.p. to explore their effects on bladder activity. The 5-HT_{1A} antagonist WAY-100635 is given as a positive control. Data are expressed as contraction interval (in

seconds) before drug application (basal), or after the application of vehicle or test article.

Continuous Slow Transvesicular Infusion (CSTI) rat Model

Male Sprague Dawley rats weighing approximately 300 g are used for the study. Rats are anaesthetized with pentobarbitone sodium (50 mg/kg, i.p). Through a median abdominal incision, bladder is exposed and a polyethylene cannula (PE 50) is introduced into the bladder through a small cut on the dome of the bladder and the cannula is secured with a purse string suture. The other end of the cannula is exteriorized subcutaneously at the dorsal neck area. Similarly, another cannula (PE 50) is introduced into the stomach through a paramedian abdominal incision with the free end exteriorized subcutaneously to the neck region. The surgical wounds are closed with silk 4-0 suture and the animal is allowed to recover with appropriate post surgical care. On the following day, the animal is placed in a rat restrainer. The open end of the bladder- cannula is connected to a pressure transducer as well as infusion pump through a three-way stopcock. The bladder voiding cycles are initiated by continuous infusion of normal saline at the rate of 100 µl/min. The repetitive voiding contractions are recorded on a Power Lab on-line data acquisition software. After an recording the basal voiding pattern for an hour, the test drug or vehicle is administered directly into stomach through the intragastric catheter and the voiding cycles are monitored for 5 hours. Micturition pressure and frequency are calculated before and after the treatment (at every 30 min interval) for each animal. Bladder capacity is calculated from the micturition frequency, based on the constant infusion of 100ul/min. The effect of the test drug is expressed as a percentage of basal, pre-drug bladder capacity. WAY 100635 is used as positive control for comparison.

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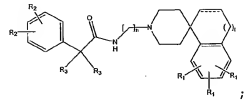
What is Claimed:

1. A compound having the structure:



;

wherein ----- is CH_2, O, -CO-, $-CO_2-$, $-CH_2-CH_2-$ or -CHCH-;

wherein t is 0 or 1, and where the cyclic ring containing t is 5 or 6-membered;

wherein n is an integer from 1 to 6 inclusive;

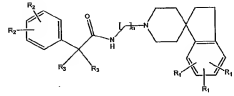
wherein each R_1 and R_2 is independently -H, -F, -Cl, -Br, -I; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, aryl or heteroaryl;

wherein each R_3 is independently -H; C_1-C_6 straight chained or branched alkyl; aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-R_2$, straight chained or branched C_1-C_7 alkyl, aryl, phenoxy or heteroaryl; and

where two R_3 moieties taken together can form a C_3-C_6 cycloalkyl;

or a pharmaceutically acceptable salt thereof.

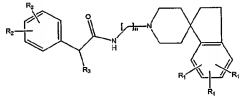
2. The compound of claim 1 having the structure:



;

wherein n, R_1, R_2 and R_3 are as defined in claim 1.

3. The compound of claim 2 having the structure:

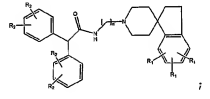


;

wherein R_3 is C_1-C_6 straight chained or branched alkyl or aryl, wherein the aryl is optionally substituted with one or more -F, -Cl, -Br, -I, $-R_2$, straight chained or branched C_1-C_7 alkyl, aryl, phenoxy or heteroaryl; and

wherein n, R_1 and R_2 are as defined in claim 1.

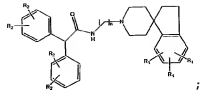
4. The compound of claim 3 having the structure:



;

wherein n, R_1 and R_2 are as defined in claim 1.

5. The compound of claim 4 having the structure:

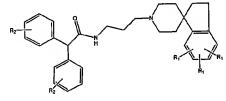


;

wherein each R_1 and R_2 is independently -H, -F, -Cl, -Br, -I; straight chained or branched C_1-C_7 alkyl, aryl or heteroaryl; and

wherein n is as defined in claim 1.

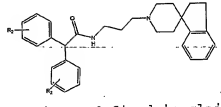
6. The compound of claim 5 having the structure:



;

wherein R_1 and R_2 are as defined in claim 1.

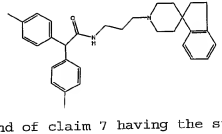
7. The compound of claim 6 having the structure:



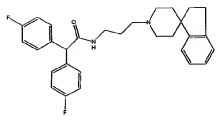
;

wherein each R_2 is as defined in claim 1.

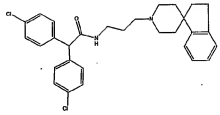
8. The compound of claim 7 having the structure:



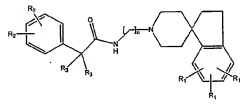
9. The compound of claim 7 having the structure:



10. The compound of claim 7 having the structure:



11. The compound of claim 2 having the structure:

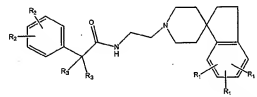


;

wherein each R_3 is independently H or C_1-C_6 straight chained or branched alkyl; and

wherein n, R_1 and R_2 are as defined in claim 1.

12. The compound of claim 11 having the structure:

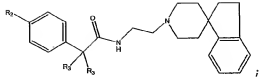


;

wherein each R_3 is C_1-C_6 straight chained or branched alkyl; and

wherein R_1 and R_2 are as defined in claim 1.

13. The compound of claim 12 having the structure:



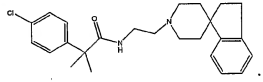
;

wherein each R_1 is F, Cl, Br or C_1-C_3 alkyl;

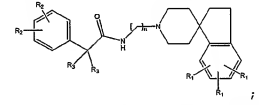
wherein each R_3 is independently H or C_1-C_7 straight chained or branched alkyl; and

wherein R_2 is as defined in claim 1.

14. The compound of claim 13 having the structure:



15. The compound of claim 2 having the structure:

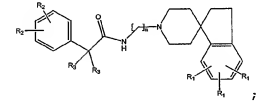


;

wherein the two R_3 moieties taken together form a C_3-C_6 cycloalkyl; and

wherein n, R_1 and R_2 are as defined in claim 1.

16. The compound of claim 15 having the structure:



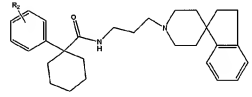
;

wherein the two R_3 moieties taken together form a C_4-C_6 cycloalkyl;

wherein each R_1 and R_2 is independently -H, -F, -Cl, -Br, -I; or straight chained or branched C_1-C, alkyl; and

wherein n is as defined in claim 1.

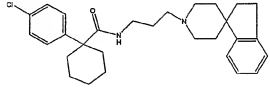
17. The compound of claim 16 having the structure:



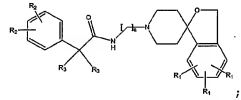
;

wherein R_2 is -H, -F, -Cl, -Br, -I.

18. The compound of claim 17 having the structure:



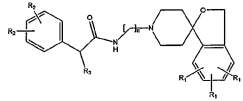
19. The compound of claim 1 having the structure:



;

wherein n; R_1, R_2 and R_3 are as defined in claim 1.

20. The compound of claim 19 having the structure:



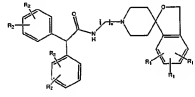
;

wherein R_3 is C_1-C_6 straight chained or branched alkyl or aryl wherein the aryl is optionally substituted

with one or more -F, -Cl, -Br, -I, $-R_2$, straight chained or branched C_1-C_7 alkyl, aryl, phenoxy or heteroaryl; and

wherein n, R_1 and R_2 are as defined in claim 1.

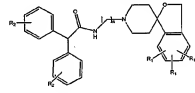
21. The compound of claim 20 having the structure:



;

wherein n, R_1 and R_2 are as defined in claim 1.

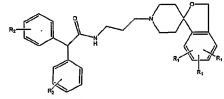
22. The compound of claim 21 having the structure:



;

wherein n, R_1 and R_2 are as defined in claim 1.

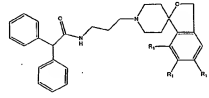
23. The compound of claim 22 having the structure:



;

wherein each R_1 and R_2 is independently -H, -F, -Cl, -Br, -I; straight chained or branched C_1-C_7 alkyl.

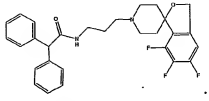
24. The compound of claim 23 having the structure:



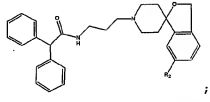
;

wherein each R_1 is independently -F, -Cl, -Br, -I; or straight chained or branched C_1-C_7 alkyl.

25. The compound of claim 24 having the structure:



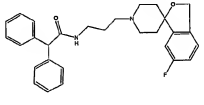
26. The compound of claim 23 having the structure:



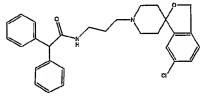
;

wherein R_1 is F, Cl, Br, I or C_1-C_7 straight chained or branched alkyl.

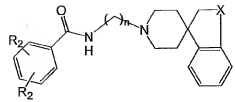
27. The compound of claim 26 having the structure:



28. The compound of claim 26 having the structure:



29. A compound having the structure:



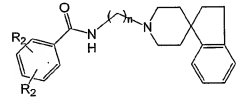
;

wherein each R_2 is independently H, F, Cl, Br, CN or C_1-C_7 straight chained or branched alkyl;

wherein X is CH_2 or O; and

wherein n is an integer from 1 to 6 inclusive.

30. The compound of claim 29 having the structure:

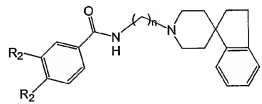


;

wherein each R_2 is independently H, F, Cl or Br; and

wherein n is an integer from 1 to 6 inclusive.

31. The compound of claim 30 having the structure:

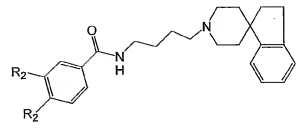


;

wherein each R2 is independently H, F, Cl or Br; and

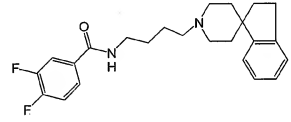
wherein n is an integer from 3 to 6 inclusive.

32. The compound of claim 31 having the structure:



wherein each R_2 is F, Cl or Br.

33. The compound of claim 31 having the structure:



34. A pharmaceutical composition which comprises a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

35. A pharmaceutical composition made by admixing a compound of claim 1 and a pharmaceutically acceptable carrier.

36. A process for making a pharmaceutical composition comprising admixing a compound of claim 1 and a pharmaceutically acceptable carrier.

37. A method of treating a subject suffering from a disorder mediated by the MCH1 receptor comprising administering to the subject a therapeutically effective amount of a compound of claim 1.

38. The method of claim 37, wherein the therapeutically effective amount is between about 0.03 and about 300 mg.

39. The method of claim 37, wherein the disorder is depression.

40. The method of claim 37, wherein the disorder is anxiety.

41. The method of claim 37, wherein the disorder is obesity.

42. The method of claim 37, wherein the disorder is urge incontinence.

43. A method of treating a subject suffering from depression, anxiety, urge incontinence or obesity comprising administering to the subject a therapeutically effective amount of a compound of claim 1.

44. The method of claim 43 wherein the therapeutically effective amount is an amount between about 0.03 and about 300 mg.

45. The method of claim 43, wherein the subject suffers from depression.

46. The method of claim 43, wherein the subject suffers from anxiety.

47. The method of claim 43, wherein the subject suffers from obesity.

48. The method of claim 43, wherein the subject suffers from urge incontinence.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/21348

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/438 ; C07D 221/20, 491/10
US CL : 514/278 ; 546/17
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/278 ; 546/17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,541,326 A (CLIFFE) 30 July 1996 (30.07.1996), example 50.	1-31
A	WO 97/45415 A1 (ROTTA RESEARCH LABORATORIUM) 04 December 1997 (04.12.1997), compounds in table 1 on pages 14-16.	1-31
A	TAKEKAWA, S. et al. T-22696: a novel, orally active and selective melanin-concentrating hormone receptor antagonist. Eur. J. Pharmacol. 2002, Vol. 438, pages 129-135, see entire document.	1-48

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 October 2003 (08.10.2003)	05 DEC 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer C. S. AULAKH Telephone No. (703) 308-0196

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